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ABSTRACT

The first section of this report on childhood tuberculosis in developed and developing countries discusses the epidemiology of tuberculosis in children. Information is presented on: (1) sources and prevalence of infection; (2) risks, frequency, and types of tuberculosis; (3) mortality rates; and (4) the relation of poverty and AIDS to tuberculosis. The second section discusses the diagnosis of tuberculosis in children, with attention to primary tuberculosus infection and several forms of acute tuberculosis, postprimary respiratory tuberculosis, and extra-respiratory tuberculosis. Inserts included in the second section concern the tuberculin skin test, chest X-rays, scoring systems and criteria for diagnosing tuberculosis, and the bacteriological diagnosis of tuberculosis. The third section examines the treatment of tuberculosis in children. Three types of chemotherapy regimens are explained, and the process of caring for a diseased child until the child recovers is outlined. Inserts included in the third section discuss antituberculosis drugs in general and Isoniazid in particular. The fourth section considers the prevention of tuberculosis in children by means of early detection, preventive chemotherapy, and the use of the vaccine BCG. The fifth section profiles an Algerian experiment to control tuberculosis by means of a 6-month regimen of daily chemotherapy. (BC)

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CHILDREN IN THE TROPICS

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CHILDHOOD TUBERCULOSIS, STILL WITH US...

1992 - N° 196-197

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ICC soon turned essentially toward Third World children and devoted its activities to the training and education of personnel with social, educational and administrative responsabilities as well as medical and paramedical workers. The desire for greater efficiency has led it to work increasingly with trainers and to concentrate its efforts on the methodological and educational aspects of mother and child care programmes.

ICC is also engaged in an attempt to further study — and — action on some aspects of the life and health of children and their family, so as to contribute to practical improvement, particularly in the fields of growth, nutrition, planned parenthood, the control of transmissible and nutritional diseases, preschool and school education, the needs of disabled and underprivileged children, etc.

Over this period of more than 30 years, a large amount of documents on children and adolescents, mostly from the developing countries, has been accumulated. This international documentation has been classified and sorted out, and has been computerized since 1983 : a bibliographic data base (BIRD : « Base d'Informations Robert Debré ») may be consulted anywhere in the world, through international communications networks. ICC also publishes periodicals, educational documents and specialized bibliographic bulletins.

As for its legal status, the International Children's Centre is a foundation under french law of recognized public utility, administered by an executive board with broad international membership.

CHILDREN
IN THE TROPICS

REVIEW OF THE INTERNATIONAL CHILDREN'S CENTRE

CHILDHOOD TUBERCULOSIS, STILL WITH US...

PIERRE CHAULET
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1992 - N° 196-197

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CHILDHOOD TUBERCULOSIS, STILL WITH US...

INTRODUCTION 5

EPIDEMIOLOGY OF TUBERCULOSIS IN CHILDREN

Tuberculous infection 7

Tuberculous disease 9
- Risk of active disease 9
- Frequency 10
- Close contact with a source of infection 11
- Active tuberculosis 13
- Bacteriologically positive pulmonary tuberculosis 14
- Other forms 15

Mortality due to tuberculosis 16

The impact of control measures 17

Poverty, AIDS and tuberculosis 17

DIAGNOSIS OF TUBERCULOSIS IN CHILDREN

Circumstances surrounding diagnosis 20

Primary tuberculous infection 20

Acute tuberculosis 22
- Tuberculous meningitis 23
- Acute miliary tuberculosis 25

Post-primary respiratory tuberculosis 26
- Pleural tuberculosis 26
- Pulmonary tuberculosis 27

Extra-respiratory tuberculosis 28
- Tuberculosis of the regional lymph nodes 28
- Osteo-articular tuberculosis 28
- Tuberculosis of serous membranes other than the pleura 29
- Urinary tuberculosis and other localizations 29

INSERTS

Household case-finding for tuberculosis 30

The standardized tuberculin test 32

A satisfactory chest x-ray 34

Scoring systems for diagnosing tuberculosis 35

Criteria for diagnosing tuberculosis in children 36

Bacteriological diagnosis 37

TREATMENT OF TUBERCULOSIS IN CHILDREN

Choice of chemotherapy regimens 42

Indications for chemotherapy regimens 45
- Chemotherapy with four drugs lasting 6 to 8 months 45
- Chemotherapy with three drugs lasting 4 to 8 months 45
- Chemotherapy with five drugs lasting 8 months 46

Care for the diseased child until recovery 48
- Pretreatment examination 48
- Informing the family 48
- Prescription of chemotherapy 48
- Direct supervision 49
- Consulting again at the end of 2 months 50
- Organization of drug distribution 50
- Checking on recovery 51
- Notification of cases of tuberculosis 51

INSERTS

Essential antituberculosis drugs 53

Isoniazid for children : 5 mg per kg is enough ! 57

Adverse effects of antituberculosis chemotherapy 59

PREVENTION OF TUBERCULOSIS IN CHILDREN

Detection and chemotherapy of infectious cases of tuberculosis 60
- Detection of sources of infection 60
- Chemotherapy of infectious cases 64

Chemoprophylaxis of tuberculosis in children 69
- Which preventive chemotherapy? 70
- Preventive chemotherapy : for which children? 70
- A special case : HIV-seropositive children 71

BCG vaccination 72
- Technical review 72
- Vaccinal technique 72

INSERT

Management of a child with a positive tuberculin test 77

AN ALGERIAN EXPERIMENT : SHORT CHEMOTHERAPY FOR TUBERCULOSIS

Material and methods 78
- Subjects 78
- Chemotherapy regimens 79

Results 80
- Tolerance and toxicity of short chemotherapy 81

INTRODUCTION*

Tuberculosis is still one of the main causes of mortality and morbidity in developing countries. Although most patients are adults in their productive years, tuberculosis also affects children, some of whom die of meningitis or acute miliary tuberculosis before the age of 5. Tuberculosis is infectious : it is transmitted to children, especially to those living in close contact with diseased adults whose sputum contains bacilli.

Tuberculosis is avoidable, however. Children are protected during their youth if they are given the BCG vaccine during the first days of life. And above all, the risk of being infected by the tubercle bacillus and of falling ill, in turn, is considerably reduced if the sources of infection within the community - that is, diseased adults - are regularly detected and properly treated.

Last, tuberculosis is curable. Chemotherapy is now capable of curing all forms of tuberculosis in almost all patients, children and adults, following a few months of treatment.

For this reason, it is important to assess the situation, and to examine the problems raised by tuberculosis in children in today's world, at a time when this disease remains a threat for children because of the persistance or extension of poverty and malnutrition, as well as of the epidemic of human immunodeficiency virus (HIV-AIDS).

The number of children affected with tuberculosis in a country depends on two main factors :

- the number (or the proportion) of children within the population ;

- the number (or rate) of bacilli-discharging individuals within this same population.

In developing countries, children under 15 represent 30 to 47 % of the overall population. In Africa and the Middle East, this figure is somewhere around 45 %. The proportion does not exceed 20 % in industrially advanced countries.

In developing countries, the number of new cases of tuberculosis with positive microscopy (otherwise known as smear-positive : patients whose sputum contains sufficient numbers of bacilli for them to be visible upon microscopic examination of expectorations) is estimated at over 3 million cases each year. Slightly over one half of these cases are regularly detected and treated.

*** By Pierre CHAULET.**

Table 1
Tuberculosis in developing countries in 1990

Regions	No. of new cases of infectious tuberculosis (estimated mean)	Cases detected (%)
Subsaharan Africa	521,000	28
North Africa and Middle East	146,000	69
Asia	2,298,000	61
South America	160,000	62
Central America and Caribbean	83,000	27
Total	3,208,000	55

Source : MURRAY C.J.L., STYBLO K., ROUILLON A. Bull. IUATLD, 1990 ; 65, 1 : 6-26.

It is easy to see that in those parts of the world with the highest numbers of children a great many cases of infectious tuberculosis develop in the population at large, and 40 to 70 % of these go undetected and untreated. In these regions, tuberculosis takes a heavy toll among children, causing suffering and avoidable deaths in the poorest families, and giving health workers the difficult job of detecting and treating diseased children.

EPIDEMIOLOGY OF TUBERCULOSIS IN CHILDREN*

When children are exposed to contagion because they live near a source of infection, a high proportion of them are infected by the tubercle bacillus : this first contact is known as primary infection. Even if they are apparently healthy, they react to an intradermal injection of tuberculin, which is proof that they have been infected.

Most of these infected children never develop tuberculous disease. However, about 10 % of them will sooner or later develop signs of this disease in the lungs or elsewhere, and especially in the lymph nodes, meninges, bones or spinal column. Some diseased children, and especially the youngest of them (under age 5 years), may die of the most serious complications of primary infection, such as meningitis or acute miliary tuberculosis.

TUBERCULOUS INFECTION

Tuberculous infection, tuberculous disease and mortality caused by tuberculosis are three individual and collective occurrences which are indicative of the impact of tuberculosis on children and also of the potential effects of specific technical control measures including the BCG vaccination of neonates and chemotherapy for identified cases.

Sources

The greatest sources of infection for children are adult patients expectorating sufficient amounts of bacilli to be visible on microscopic examination of sputa : that is, cases of smear-positive pulmonary tuberculosis. This fact has been clearly demonstrated in populations where mass BCG vaccination has never been implemented.

In Canada, for instance (British Columbia and Saskatchewan), between 1966 and 1971 (1), the prevalence of the infection (that is, the percentage of children reacting to tuberculin) was higher at all ages in children living in close contact with smear-positive tuberculous patients than in children living with other categories of patients or in the population at large.

In Rotterdam, between 1967 and 1969 (2), the prevalence of the infection was 50 % in 0 to 14 year-olds living in close contact with smear-positive patients, whereas it was only 6 % for those in close contact with smear-negative patients and much lower for other types of contact or in the population at large.

(1) GRZYBOWSKI S., BARNETT G.D., STYBLO K. Contacts of cases of active pulmonary tuberculosis. Bull. Int. Un. Tuberc. 1975 ; 50, 1 : 90-106.

(2) VAN GEUNS H.A., MEIJER J., STYBLO K. Results of contact examination in Rotterdam - 1967-1969. Bull. Int. Un. Tuberc. 1975 ; 50, 1 : 107-121.

*** By Pierre CHAULET.**

Table 2

Prevalence of the infection in 0 to 14 year-olds living in close contact with a source of infection and in the population at large in British Columbia and Saskatchewan

Age group of contact subjects (years)	Bacteriological status of the source of infection			Prevalence of infection in same age groups in the population at large
	Positive micro-scopy	Positive culture	Negative culture	
0 - 4	35	13	7	0.7
5 - 9	43	18	16	0.9
10 - 14	52	31	23	2.2

Source : Ibid. 1.

Prevalence

The prevalence of the infection in children under 15 within a population reflects the number of sources of infection within this population, and the intensity of transmission of the bacillus. Indeed, transmission of the infection is encouraged by promiscuity and overcrowded living conditions, as well as by malnutrition which reduces resistance to infections.

In 1960, a very high prevalence of the infection was recorded in the Inuit population of North-Western Canada : 50 % of 6 year-olds, at a time when the rate of new cases of bacillary tuberculosis in the population at large was 593 for 100,000 inhabitants. In 1987, following the implementation of active screening and treatment measures, and the considerable reduction in the number of new cases of bacillary tuberculosis in the population at large, the prevalence at age six had dropped to less than 5 % (3).

In developing countries, the present rate of prevalence of infection in un-BCG-vaccinated 14 year-olds is often above 20 %. At age 10 it is usually somewhere between 10 and 20 %.

Annual risk of infection

The annual increase in prevalence of the infection rises with the number of sources of infection within the community. This increase, usually calculated over a span of several years and compared to the mean annual increment, expresses the annual incidence of the infection, also called the annual risk of tuberculous infection. The annual risk of infection represents the percentage of individuals first infected in the course of the year.

There is a close link between the annual risk of tuberculous infection and the number of sources of infection present within the population at large. For each 1 % of annual risk of tuberculous infection it is estimated that there is an annual incidence of about

(3) STYBLO K. Epidemiology of tuberculosis, Infektions Krankheiten und ihre Erreger, Band 4/VI, VEB Gustav Fischer Verlag, Jena 1984.

50 new cases of smear-positive tuberculosis per 100,000 inhabitants (39 to 59 cases in the 95 % confidence interval) (4).

For a population of 100,000 inhabitants, 45 % of whom are under 15, a 1 % annual risk of infection means that about 450 of the 45,000 individuals aged 0 to 14 will be infected each year, most of them in a latent form (symptom-free primary infection) (5).

The annual risk of tuberculous infection varies enormously from one part of the world to another and from country to country. The number of natural primary infections is therefore higher in those countries where the annual risk of infection with tuberculosis is high, and particularly when a high proportion of children under 15 have not received the BCG vaccine. It is a known fact that in the absence of chemotherapy a source of infection remains contagious for an average of two years, and contaminates about 10 to 13 persons a year. At present, a varying proportion of sources of infection in many developing countries is neither detected nor treated, and in such situations, a person expectorating bacilli who goes undetected may infect (or reinfect) at least 20 people (6).

Conversely, as soon as chemotherapy is administered, sources of infection become less contagious in a matter of weeks : for this reason, each source of infection only contaminates 2 to 3 people during the period prior to diagnosis and treatment. When a large proportion of sources of infection is detected and treated, this quite naturally leads to a lowered annual risk of infection, which is evidenced within a few years.

This explains why the lowered risk of infection is linked with the thoroughness with which screening and treatment measures are applied within a given community : this drop varies considerably from one country to another ; it is still slow in precisely those regions where tuberculosis is most frequent, where the annual risk of infection is highest and the proportion of cases detected is lowest.

TUBERCULOUS DISEASE

RISK OF ACTIVE DISEASE

The risk of having infection turn into active disease is about 10 %, but there is actually not any stable figure. The risk of developing tuberculous disease is estimated to be between 5 and 15 % during the first ten years after primary infection, with the risk at its highest during the first two years, and dependent on a number of factors such as age at occurrence of primary infection, the nutritional status of the infected child, the bacteriological status (that is, the amount of bacilli in the expectoration) of the source of infection and above all, the intensity of contacts between the infected child and the source of infection. These factors explain why the risk of developing an active case of tuberculosis is high in

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(4) MURRAY C.J.L., STYBLO K., ROUILLON A. Tuberculosis in developing countries : burden, intervention and cost. Bull. Int. Un. Tuberc. 1990 ; 65, 1 : 6-26.

(5) STYBLO K. The epidemiology of tuberculosis in children, TSRU/IUATLD. Progress Report 1991 ; 1 : 175-183.

(6) Ibid. 3.

developing countries as well as among the underprivileged classes in industrialized countries.

Table 3
Estimated annual risks of tuberculous infection and their trends in various countries

Area	Estimated annual risk of tuberculous infection %	Estimated annual decrease in risk of infection %
Subsaharan	1.5 - 2.5	1 - 2
Asia	1- 2	1 - 3
Central America and Caribbean	0.5 - 1.5	1 - 3
South America	0.5 - 1.5	2 - 5
North Africa and Middle East	0.5 - 1.5	5 - 6
Europe, North America	0.2 - 0.02	10 - 13

Source : Ibid. 4.

To return to the above-mentioned example : in a population of 100,000, if the annual risk of tuberculous infection is 1 %, an estimated 45 of the 450 infected children will have respiratory or non-respiratory signs of tuberculous disease, and these will occur before or after age 15, depending on the age at which primary infection developed.

FREQUENCY

There are two ways of measuring the frequency of tuberculous disease in children :

- either in comparison with all reported cases of tuberculosis within the community ;

- or in terms of number of patients per 100,000 children of the same age group.

Childhood tuberculosis only represents a small fraction of reported cases of tuberculosis in any given country. In industrialized countries, where children represent about 20 % of the overall population, the percentage of cases of tuberculosis in children among all registered cases is 2.5 % in Japan (1981), 5.2 % in the USA (1987) and 7 % in Great Britain (1977-1978) (7). In developing countries, where 45 % of the overall population are children, the percentage of cases of tuberculosis in children in comparison with all cases of tuberculosis is 8.8 % in Algeria (1984), 9 % in Tunisia (1983), 17.7 % in Kenya (1974) and 18.5 % in Tanzania (1980) (7).

(7) ANANE T. Problèmes posés par la tuberculose de l'enfant en Algérie. Perspectives d'avenir. DESM Thesis. Algiers : mimeographed, 1987 : 201 p. plus appendices.

Morbidity rate

Rates of tuberculous morbidity in children vary considerably from one country to another and within a given country depending on the socio-economic conditions prevailing in different communities or social groups. In Great Britain, for instance, in 1978-79 (8), rates of tuberculous morbidity in children were much higher in ethnic minority groups (whose living conditions and income are usually less satisfactory) than in the white population. For 100,000 children, the annual rate of new cases was 21.1 in West Indians, 90 in Indians, 130 in people from Pakistan or Bangladesh and 3.6 in whites. The overall figure for England was 7.

Similarly, in the USA, in 1985 (9), rates of incidence of tuberculosis were higher among minority groups, especially for children under 5.

Table 4

Tuberculosis morbidity among children in the United States in 1985

Ethnic groups	Rate per 100,000	
	0 - 4 years	5 - 14 years
Whites (except Spanish-Americans)	1.3	0.4
Blacks	10.5	3.3
Spanish-Americans	11.7	3.5
American Indians	17.2	8.2
Overall	4.4	1.4

Last, the age breakdown of tuberculosis may differ with the structure of the population, the intensity of transmission of tuberculosis within the population and the BCG vaccination policy implemented (10) (11).

CLOSE CONTACT WITH A SOURCE OF INFECTION

Tuberculous disease is more frequent in children living in close contact with a source of infection. In Madras (Southern India), in an extremely poverty-stricken population with highly promiscuous living conditions, people who were in close family contact with bacteriologically positive tuberculous patients (about 90 % of which cases were treated and cured) were studied over a 5-year period. Two consecutive studies were conducted in 1966 and 1970 (12, 13) on different groups. Of the individuals of all ages who lived in contact with patients, 11.7 % of those in the first study and 8.8 % of those in the second one developed active tuberculosis within the five years subsequent to the infecting

(8) Ibid. 4.

(9) SNIDER D.E., RIEDER H.L., COMBS D., BLOCH A.S., HAYDEN C.H., SMITH M.H. Tuberculosis in children. Pediatr. Infect. Dis. 1988 ; 7, 4 : 271-278.

(10) STYBLO K., SUTHERLAND I. The epidemiology of tuberculosis in children. Bull. Int. Un. Tuberc. 1982 ; 57 : 134-149.

(11) Ibid. 7.

contact (over half during the first year). In both studies, the proportion of children under 5 at the time of infecting contact - most of whom were tuberculin-negative when first examined - and who developed active tuberculosis, was higher - 25 % and 20 % - than in the other age groups.

Table 5
Age breakdown of tuberculous morbidity
in England and Algeria

Countries Ethnic groups	Annual rate per 100,000 Age breakdown (years)				
	0 - 4	5 - 9	10 - 14	0 - 14	15 and over
England 1978					
Whites	3.6	4.7	2.7	3.6	11
Asians born :					
in England	74	67	113	80	44
in Asia	144	169	203	183	
Algeria 1984	5.6	14.4	25.4	12.7	113

Source : Ibid. 7 and 10.

In Canada (British Columbia and Saskatchewan), between 1966 and 1971, children living in contact with tuberculous patients were carefully examined within six months of diagnosis of the disease (14).

Children under 14 who were already infected were examined to determine what proportion of them had developed active tuberculosis, and among these, the proportion with bacteriologically confirmed disease, taking into account the degree of contact with patients (close or occasional contact) and the bacteriological status of the source of infection.

38 % of children in close contact and 25 % of those in occasional contact with smear-positive tuberculosis patients were found to have developed active tuberculosis, with bacteriologically confirmed cases of pulmonary tuberculosis in 13 % and 8 % respectively.

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(12) KAMAT S.R., DAWSON J.J.Y., DEVADATTA S. et al. A controlled study of the influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in South India. Bull. Wld. Hlth. Org. 1966 ; 34 : 517-532.

(13) DEVADATTA S., DAWSON J.J.Y., FOX W. et al. Attack rate of tuberculosis in a 5-year period among close family contacts of tuberculous patients under domiciliary treatment with isoniazid plus PAS or isoniazid alone. Bull. Wld. Hlth. Org. 1970 ; 42 : 337-351.

(14) Ibid. 1.

Table 6
Cases of active tuberculosis developing during a 5-year period in persons in contact with a bacteriologically positive source of infection in Madras

Age at admission to the study	1966 study			1970 study		
	Contacts	Contacts who developed active tuberculosis		Contacts	Contacts who developed active tuberculosis	
		No.	%		No.	%
0 - 4	101	25	25	147	29	20
5 - 14	163	15	9	254	21	8
15 and over	264	22	8	474	27	5.7
Total	528	62	11.7	875	77	8.8

Source : Ibid. 12 and 13.

ACTIVE TUBERCULOSIS

Active tuberculosis in children is the sum of clinical signs indicative of the active proliferation of bacilli once they have first entered the body. The frequency and seriousness of these signs are quite variable, and are related to the natural history of tuberculosis in the child (15).

Primary infection

For a minority of infected children, who always have a positive skin reaction to tuberculin, primary infection takes the form of a primary complex (primary lesion at site of entrance and hilar lymphadenopathy), visible on x-rays. These radiological signs are occasionally accompanied by systemic signs (a grippe-like syndrome lasting one or two weeks) or muco-cutaneous signs. Three types of complications may ensue :

Complications

- benign, local complications : segmental densities caused by obstruction of a small bronchus during lymphadenopathy, observed in one out of five patent primary infections in young children (usually before age 5) within six months of primary infection, pleurisy, especially in older children, within a year of primary infection ;

- severe haematogenous complications, caused by dissemination of the bacilli in the blood stream, leading to systemic miliary disease or meningitis (occasionally in conjunction with the former). These complications develop within 9 months of primary infection, and usually in children under 2 ;

- other less serious haematogenous complications, or extra-pulmonary forms of tuberculosis : regional lymphadenitis (mostly cervical), osteo-articular tuberculosis occurring during the first years after primary infection, peritoneal, pericardial and exceptionally,

(15) GRZYBOWSKI S. Natural history of tuberculosis (Personal communication, 1990).

urogenital tuberculosis, which may be seen several years after primary infection, more often in adolescents and young adults than in children.

Post-primary pulmonary tuberculosis

Post-primary pulmonary tuberculosis is an unusual complication in children : it develops in about 4 % of those whose primary infection occurred before age 5, and generally develops several years later, after age 10. Conversely, it is more frequent (and more precocious) in children whose primary infection took place between ages 12 and 14 : it is then recorded in 10 % of cases, and develops within 2 years of primary infection.

These findings explain why the first two years after primary infection represent a critical period, during which children under 5 may develop local or severe haematogenous complications of primary infection, while adolescents are susceptible to post-primary pulmonary tuberculosis.

They also explain why active tuberculous disease in children is rarely confirmed by bacteriological examination of sputa (microscopy, or when feasible, culture). Diagnosis is based on a combination of facts : clinical history, knowledge of contact with a source of infection, reaction to tuberculin, physical and radiological examination. Reporting of cases of tuberculosis in children is often underestimated in developing countries, owing to gaps in health coverage and to lack of access to radiological facilities for people living in outlying areas.

14

BACTERIOLOGICALLY POSITIVE PULMONARY TUBERCULOSIS

Cases of infectious pulmonary tuberculosis, and especially smear-positive cases, which represent the main sources of transmission of the infection, only constitute a small fraction of cases of tuberculosis in children. This has been shown by a study of cases of tuberculosis in children in the Netherlands and in Norway, before the chemotherapy era, in 1951-53, when bacteriologically positive cases of pulmonary tuberculosis represented 0.5 to 2.7 % of notified cases, depending on the age group, in the Netherlands, and from 4.7 % to 13.4 % of notified cases in Norway (16). This is the situation that currently prevails in developing countries. Most cases of tuberculosis in children, then - 87 to 97 % - are not infectious.

In Saskatchewan (17), testing for bacilli was done routinely on contact children (by gastric lavage on three occasions, which is normally not done routinely). Even then, the proportion of smear-positive cases was only 2 % of all cases, whereas the proportion of positive cultures was 29 %.

These findings show that tuberculosis in children has a very limited effect on the epidemiological situation of the community. Although it is a cause of considerable human suffering and contributes to infant mortality when it is not diagnosed and its severe haematogenous complications are not treated, it makes only a

(16) Ibid. 3.
(17) Ibid. 3.

minor contribution to the number of sources of infection within a community (18,19).

Table 7

Bacteriologically positive tuberculosis in 0-14 year-olds living in contact with a case of tuberculosis in Saskatchewan (1960-1973)

Type of tuberculosis	No.	%
pulmonary, smear-positive	7	2
pulmonary, positive culture only	103	29
pulmonary, negative culture	205	57
extra-pulmonary	44	12
Total	359	100

OTHER FORMS

The distribution of forms of tuberculous disease in children is quite variable in developing countries, depending on the diagnostic means available and on the diagnostic criteria applied by grassroots health workers, as well as on the BCG vaccinal coverage of children and the care received by adult patients.

Nevertheless, it may be estimated that :

15

- in 50 % of cases, the disease is a patent primary infection, with radiologically visible mediastinal lymphadenopathy, with or without ventilation disorders, especially in the youngest children (ages 0 to 4) ;

- in approximately 30 % of cases, the disease is extra-pulmonary : meningitis and/or miliary tuberculosis, resulting from early haematogenous dissemination, especially in children under 5, with pleurisy more frequent in children over 5, and tuberculosis of the regional lymph nodes, bones and joints or spinal column at all ages ;

- in about 20 % of cases, the disease is focalized in the lungs. This post-primary pulmonary tuberculosis usually develops after age 5. It is bacteriologically confirmed in about half of cases, especially in older children, between ages 10 and 14.

In Algeria, during a prevalence survey (20) conducted in 1984 in an area with 5.6 million inhabitants (including 18 % of children under 5 and 46 % under 15), where BCG vaccination at birth had covered over 90 % of the population for several years, the proportion of primary infections in general and of various forms of tuberculosis in children under 5 was found to be low.

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(18) Ibid. 5.

(19) Ibid. 10.

(20) Ibid. 7.

Table 8
Age breakdown of forms of tuberculosis in Algeria (1981 prevalence survey)

Forms	Age groups (years) 0 - 4		5 - 9		10 - 14		Total 0 - 14	
	No.	%	No.	%	No.	%	No.	%
Patent primary infection*	46	41	53	26	38	13	137	22
Pleurisy	4	4	18	9	24	8	46	8
Miliary	2	2	6	3	1	0.5	9	2
Meningitis	3	3	2	1	1	0.5	6	1
Other type of extra-pulmonary tuberculosis	39	34	64	31	107	36	210	34
Pulmonary tuberculosis	18	16	61	30	123	42	202	33
Total	112	100	204	100	294	100	610	100

** With mediastinal adenopathy visible on chest x-ray at least.*

MORTALITY DUE TO TUBERCULOSIS

It is difficult to study mortality due to tuberculosis in children in developing countries, where diagnostic techniques are lacking, a variable fraction of the population has no access to health services, and the notification system is deficient.

A study of data recorded in the Netherlands between 1911 and 1940, before the chemotherapy era, at a time when the annual risk of infection was extremely high in that country (8.7 % before 1920, 3 % between 1931 and 1940) may yield some indication, however. By comparing the rates of mortality due to all forms of tuberculosis and to tuberculous meningitis per 100,000 children, and the corresponding annual risk of infection in different age groups, K. STYBLO (21) was able to show that the highest mortality rates were always seen before age 5 years, mostly because of the frequency of tuberculous meningitis.

In a context where children were not given the BCG and patients did not receive chemotherapy, the estimated mortality rates (for all forms, taken together) were 17 per 100,000 children aged 0 to 4 years, and 7 per 100,000 for 5 to 14 year-olds for an annual risk of tuberculous infection of 1 %. Mortality rates for tuberculous meningitis were respectively 9 and 3 per 100,000 children in each age group.

These figures are only useful for estimation purposes. They definitely cannot be applied indiscriminately to the present situation in developing countries, for two major reasons. The first is that in the Netherlands, even before 1940, the vast majority of cases of tuberculosis in children were detected, and diseased children were taken away from sources of infection and hospitalized, and although treatment was then of limited efficacy it did make it possible to reduce mortality from extra-pulmonary tuberculosis (with

(21) Ibid. 5.

the exception of meningitis). Furthermore, at present, most children in developing countries are given the BCG during the first years of life. BCG vaccination therefore avoids natural primary infection and its severe haematogenous complications in young children. In addition, a varying proportion of sources of infection (that is, of diseased adults) are given chemotherapy, which also helps to reduce mortality due to tuberculosis in children.

THE IMPACT OF CONTROL MEASURES

The main technical measure used to control tuberculosis is the ongoing detection of sources of infection within the community (case-finding), followed by proper chemotherapy in confirmed cases. This not only makes it possible to cure patients, but also considerably reduces the number of sources of infection, the transmission of the bacillus and the annual rate of tuberculous infection within the community. Children are the first beneficiaries of this measure.

Further, in developing countries, mass BCG vaccination, administered at birth or within weeks of birth to uninfected children diminishes the number of cases of tuberculosis, and especially of patent primary infections and their severe haematogenous complications - meningitis and miliary tuberculosis - in children under five. It therefore has a major direct effect on children, but its indirect effect is minor : although it does avoid the occurrence of a few cases of post-primary pulmonary tuberculosis in adolescents and young adults, these "avoided" cases only represent a tiny fraction of the sources of infection within the community. This explains why the BCG vaccination of small children has no (or almost no) effect on the transmission of the infection within the community, or on the annual risk of infection.

Last, chemoprophylaxis, applied to apparently healthy but actually recently infected children, cuts down the risk of transition from infection to disease. It may be administered to exposed groups in low-prevalence countries. It does not constitute a basic measure for the tuberculosis control programme in developing countries, where curative chemotherapy is not administered to all cases present within the community, for lack of adequate case-finding, and is occasionally not even carried through to its term in identified cases, owing to a shortage of drugs or a deficient drug supply and distribution system.

POVERTY, AIDS AND TUBERCULOSIS

Two factors may increase the impact of tuberculosis in children in the coming decade : the extension of poverty and the global HIV epidemic.

Since the early 1980s, the worldwide economic crisis has struck people everywhere, but the developing countries have been more seriously affected. The number of very poor countries (also known as the "least advanced nations") has doubled in one decade, reaching 42 countries in 1990, most of these being located in subsaharan Africa, southern Asia and Central America. A considerable drop in production levels and in standards of living has been recorded in all developing countries, along with a devaluation of local currencies, an increase in national indebtedness, and a reduction in governmental budgets, more particularly in welfare

Economic situation

budgets. In the global context of increasing inequality, with cutbacks in the amount of money devoted to health, the first to be affected are the poorest and most vulnerable strata in each country. The agreements signed by governments in Alma Ata in 1977, for the development of primary health care, have not always been honoured, although there have been some successful national programmes. Inappropriate tuberculosis control strategies had not yet been corrected before the onset of the crisis, at a time when financial resources were relatively more abundant. The cuts in health budgets have resulted in a decrease in primary health activities, and reductions in basic health personnel. The devaluation of local currencies and the lack of hard currencies have complicated the importation of antituberculosis drugs, microscopes and radiology equipment. In many countries, people are now obliged to pay for the detection and treatment of tuberculosis, although patients belong to the most poverty-stricken strata of society.

World Bank experts (22) forecast a reduction in the number of poor people in southern Asia by the year 2000, but a rise in their number in subsaharan Africa. To this must be added famines, local or international conflicts, various social conflicts and population movements which further complicate the organization of health services and their availability. All of these factors necessarily contribute to maintaining tuberculosis as a threat for the peoples of developing countries, and more specially for children in the most underprivileged classes.

☐ *Aids*

The rapid extension of the HIV epidemic in subsaharan African countries first, and more recently in certain countries in south-east Asia and South America, will definitely contribute (23, 24) to a worsening of the tuberculosis problem in developing countries. Because of the immune deficiency it causes in seropositive individuals, the HIV epidemic increases the risk of tuberculosis. An increased incidence of infectious tuberculosis has already been reported in Africa : the increment imputable to the VIH infection is as high as 20 % of the incidence of notified cases in Kenya, 40 % in Tanzania and Zaire, 100 % in Uganda. In many countries in subsaharan Africa, an increased incidence of tuberculosis is foreseeable in the 15 to 49 year-old age group, in direct relationship with the seroprevalence of the HIV (25).

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(22) World Bank staff : World Development Report. Poverty ; Washington, 1990.

(23) TEN DAM H.G., ERIKI P. Surveillance of the tuberculosis/HIV problem. TSRU/IUATLD Progress Report. 1989 ; 3 : 1-5.

(24) STYBLO K. The potential impact of AIDS on the tuberculosis situation in developed and developing countries. Bull. Int. Un. Tuberc. 1988 ; 63, 2 : 26-29.

(25) SCHULZER M., FITZGERALD J.M., ENARSON D.A., GRZYBOWSKI S. An estimate of the future size of the tuberculosis problem in subsaharan Africa resulting from HIV infection. TSRU/IUATLD Progress Report. 1991 ; 3 : 28-47.

The worldwide epidemic of HIV will therefore have at least two consequences on tuberculosis in children in these countries :

- an increased risk of tuberculosis in certain children contaminated by the HIV, because they will be born to seropositive mothers ;

- an increased risk of infection by the tubercle bacillus because of the foreseeable increase in the number of sources of infection in these countries.

Conclusion

Between the present time and the turn of the century, the tuberculosis problem will grow worse in the developing countries. Contrary to the optimism that prevailed in the early 1980s, it is now clear that children as well as adults will still stand unequal as to their chances of access to health in the year 2000.

For this reason it is important to choose the most effective means presently available in the fight against tuberculosis, and to strengthen national antituberculosis programmes so as to limit the impact of those inequalities which have increased over the past ten years.

DIAGNOSIS OF TUBERCULOSIS IN CHILDREN*

It is often difficult to diagnose tuberculosis in children, since doctors tend to confuse diagnosis of tuberculous infection, which is usually latent, and that of the disease tuberculosis, which takes the form of clinical and/or radiological signs.

In this chapter, only the problem of the diagnosis of the disease tuberculosis in children will be discussed ; that is, of cases of tuberculosis which must be notified and receive curative chemotherapy (26, 27, 28).

CIRCUMSTANCES SURROUNDING DIAGNOSIS

There are two main circumstances in which tuberculosis may be diagnosed in a child :

- either the child presents symptoms which worry the parents : he/she is then brought to a consultation in a clinic or a hospital ;

- or the child does not suffer from any symptom but is examined, at home or at a clinic, during a routine case-finding visit for all individuals in household contact with an infectious case of tuberculosis.

Irrespective of the circumstances surrounding its discovery, tuberculosis in children may take on extremely different forms :

- primary tuberculous infection or primary tuberculosis ;

- acute tuberculosis : meningitis and acute miliary tuberculosis ;

- post-primary respiratory tuberculosis : pulmonary and pleural forms ;

- extra-respiratory tuberculosis.

PRIMARY TUBERCULOUS INFECTION

Primary tuberculous infection may be seen at all ages, but essentially before age five in children who have not been given the BCG. The younger the child, the greater the severity of the local complications and the risk of dissemination.

These primary infections are usually asymptomatic and may go unnoticed, seemingly a passing flu. They may be characterized by a low-grade fever, pallor, general fatigue and loss of appetite. In some rare cases they are more visible, with signs suggestive of typhoid fever : high fever, around 39-40°C, with severe asthenia but no digestive disorders.

In other cases, muco-cutaneous symptoms are most prominent :

- erythema nodosum : nodules, red at first then ecchymotic, painful spontaneously or when touched, occurring in two or three successive patches on the inner side of the legs, the rear side of the forearms and occasionally on the forehead ;

(26) STARKE J.R. Modern approach to the diagnosis and management of tuberculosis in children. Ped. Clin. North Am. 1988 ; 35, 3 : 441-464.

(27) Ibid. 9.

(28) MILLER F.J.W. Tuberculosis in children. Med of the Tropics ; Churchill Livingstone, 1982.

*** By Tahar ANANE and Jean-Paul GRANGAUD.**

- phlyctenular kerato-conjunctivitis : a small, yellowish nodule infiltrating the conjunctiva, inserted on the edge of the cornea, surrounded by a conjunctival vascular network.

No matter what the clinical signs, even when they are discrete or silent, primary infection is evidenced by definite anomalies seen on a chest x-ray. Three types of abnormal pictures may be seen on a high-quality full-face x-ray :

Hilar or mediastinal adenopathy

- most frequently, a simple, unilateral hilar or mediastinal lymphadenopathy, a clearly outlined round or oval opacity shadowing the hilar vessels or in the right latero-tracheal region, with no anomaly visible on the pulmonary parenchyma ;

Primary complex

- or a typical primary complex, combining a hilar or mediastinal lymphadenopathy and, on the same side, the primary lesion at the parenchymal site of entrance : a nodule 3 to 10 mm in diameter, with fuzzy margins, located on the lower part of the upper lobe (near the median incisure, on the right) or at the base, 1 to 2 cm above the diaphragm. Occasionally this nodular density is encompassed in a less dense shadowy area, with fuzzy margins. Thin lymphangitic streaks may link the primary lesion to the lymphadenopathy ;

Segmental density

- or again, in about 20 % of cases, a hilar adenopathy along with a segmental density (occasionally lobar in infants). This diffuse density, with straight margins on full-face and profile x-rays, is indicative of a ventilation disorder due to obstruction of a bronchus by mediastinal lymphadenopathy. It may partially mask the adenopathy of which it is the consequence, and totally mask the primary lesion. Segmental densities are usually located in the ventral segment of the upper right lobe or of the left culmen, in the middle lobe or the lingula, or in the ventral segment of the lower lobe. They are particularly frequent when the primary infection affects a very young child. Unilateral, obstructive emphysema caused by bronchial obstruction is exceptional.

In every case, these radiological signs, with or without any clinical signs, call for :

Search for a source of infection

- a search for a source of infection living under the same roof as the child : it is found in nearly 80 % of cases in children under 5, and in 50 % of cases in older children ;

Tuberculin test

- a tuberculin test : within 3 days, the intradermal injection of purified PPD tuberculin (RT23 or IP48) induces an induration greatly exceeding 5 mm, and usually comprised between 8 and 15 mm.

The combination of characteristic radiological anomalies and of a positive tuberculin test authorizes the diagnosis of a primary tuberculous infection in a non-BCG-vaccinated child, particularly when he/she is in contact with a source of infection at home.

In children with a vaccinal BCG scar and a strongly positive tuberculin test, primary infection can only be diagnosed when the radiological pictures are typical, and once all other causes of mediastinal densities have been eliminated. The latter include thymal hypertrophy in infants under two, and hodgkins or non-hodgkins

lymphoma (densities are generally larger, bilateral and asymetric) in older children.

Evolution

Primary infection lesions usually follow a benign course, tending to disappear or to achieve calcification, but they may occasionally develop local complications :

Fistulization

- the size of the lymphadenopathy increases, it softens and fistulizes in the bronchi, draining its liquefied caseous contents into these. This fistulization, which occurs between the 4th and the 7th month of existence of the adenopathy, is accompanied by a cough and the discharge of bacilli in the sputa. The lymphatic fistula closes up within several weeks ; a small, benign tumour occasionally develops on its outskirts : this is an endobronchial granuloma, which more or less completely obstructs the bronchial lumen and may cause atelectasis in the corresponding pulmonary territory ;

Primary cavity

- if the primary lesion at the site of entrance is large, it may undergo caseation, liquefy and drain into the bronchi, thus producing a primary cavity with expectoration of bacilli in the sputa. This is rare ;

Atelectasis

- last, if lymph-node obstruction persists in the absence of treatment, or if an obstructive, endobronchial granuloma develops, a segmental density may turn into atelectasis with concave margins, within which local bronchiectasis occurs if bronchial obstruction lasts more than three months. The combination of hilar calcifications and focal, ipsilateral bronchiectasis, along with repeated haemoptysis ("hilar disease") is a distant mechanical sequel of primary infection.

These complications fall into two categories :

- those which are signs of infectious, active complication of primary tuberculous infection (endobronchial fistulization of the lymph-node caseum, formation of primary cavitation), which may reveal its existence, are accompanied by the presence of bacilli in the sputa and require antituberculosis chemotherapy ;

- those which are late, mechanical sequelae of primary infection (hilar or pulmonary calcifications, as well as bronchiectasis), and are not signs of active tuberculosis ; they do not require antituberculosis chemotherapy, even if they are accompanied by haemoptysis or are fixation points for repeated bacterial respiratory infections, but not for tuberculosis.

ACUTE TUBERCULOSIS

Tuberculous meningitis and acute miliary tuberculosis are two early complications of primary infection which are particularly serious because they are fatal if they go unrecognized ; when diagnosed at too late a date they may also leave major sequelae. They are linked to the dissemination of the tubercle bacilli from the primary infection lesions, through the blood stream. They are observed at all ages, but especially in young, non-BCG-vaccinated children : before age two years, 5 to 10 % of the latter develop meningitis or miliary tuberculosis, whereas the frequency of these complications tends to drop in children who are infected later.

TUBERCULOUS MENINGITIS

Tuberculous meningitis occurs between 2 and 12 months after primary infection, and is announced by irregular fever, character disturbances and moodiness : the child ceases to play, becomes irritable, sleeps poorly at night and is sleepy all day.

The major signs develop within one week : fever exceeding 38°C, headaches, vomiting. Examination shows stiffness of the neck and occasional neurological signs such as strabismus, ptosis, convulsive seizures. When it goes undiagnosed, consciousness is gradually impaired to the point of coma, the meningeal syndrome is complete and the neurological disorders progress. When diagnosed too late, functional sequelae of varying severity occur, including several forms of paralysis, deafness and blindness. It is therefore essential that the complementary examinations necessary for diagnosis be performed as soon as the first presenting signs occur :

Chest x-ray

- a high-quality full-face chest x-ray may be normal or show a hilar adenopathy or a primary complex or again, in 20 % of cases, be indicative of miliary pulmonary tuberculosis ;

Fundus of the eye

- fundus of the eye, difficult to perform in children, may show the presence of choroidal tubercles - yellowish nodules disseminated throughout the choroid - sometimes raising the retinal vessels. These nodules are indicative of haematogenous dissemination, and are seen in 80 % of cases of associated miliary pulmonary tuberculosis and more rarely (in 20 % of cases) in the absence of any pulmonary miliary lesion ;

Lumbar puncture

- lumbar puncture is the decisive test : it should be performed rapidly, and repeated when necessary, so as to enable cytochemical analysis of the cerebrospinal fluid and to ascertain the presence of the tubercle bacillus.

The cerebrospinal fluid is clear or opalescent, hypertensed, rich in lymphocytes (30 to 300 cells per mm^3), the albumin concentration is above normal (0.6 to 2 g/l) and this increment has prognostic value. The glucose concentration is low (between 0.40 and 0.20 g/l). The tubercle bacillus is rarely evidenced by direct examination : only culturing of three specimens of CSF taken on three consecutive days (either by lumbar puncture or by sub-occipital puncture) secures identification of the bacillus in 90 % of cases.

This means that diagnosis of tuberculous meningitis (with the subsequent immediate implementation of effective, specific chemotherapy) is based on presumptive clinical, radiological and biological evidence : it must be made before the CSF culture yields its findings, and even before the tuberculin test result - actually often negative - is available. When these presumptive elements are present, a complete course of curative chemotherapy must be instituted immediately, without awaiting isolation of the tubercle bacillus.

Specialized complementary tests such as electroencephalography and above all, computed cerebral tomography cannot be a part of everyday practice. They are not of diagnostic value, and are only useful in proving that the infectious process is spreading on the surface of the cerebral parenchyma and inside it, and in evaluating complications such as hydrocephalus.

Taken together, the clinical and biological signs are sufficient for differentiating tuberculous meningitis from other types of clear-fluid meningitis in children, the main examples of which are acute viral meningitis and acute bacterial meningitis attenuated by anti-biotherapy.

Table 9

Differential diagnostic criteria for clear-fluid meningitis in children

Forms	Clinical signs	Biological signs CSF	Microbiological diagnosis
Tuberculous meningitis	Onset 1-2 weeks Absence of BCG vaccination Neurological signs	Lymphocytes 30-300/mm³ Albumin 0.6 - 2 g Glucose 0.4 - 0.20 g	Positive culture at 3 weeks (90 % of cases)
Viral meningitis	Onset 1-2 days No neurological signs	Lymphocytes 200-1,000/mm³ Albumin 0.20-0.30 (N) Glucose 0.50-0.80 (N)	Mumps Enterovirus Myxovirus, Adenovirus, laboratory-evidenced
Meningo-coccal meningitis at onset	Begins with rhinopharyngitis Sudden onset Herpes purpura	Impaired polymorphonuclears 200 to 500 mm³ Albumin 0.4-0.5	Intra and extra-cellular meningococci on direct examination
Attenuated bacterial meningitis	Attenuated meningeal syndrome	Impaired polymorphonuclears Albumin over 0.8 Glucose under 0.4	Germs on direct examination and in culture
Meningism during infections	Silent meningeal syndrome	Fewer than 10 cells/mm³ Albumin 0.20-0.30 Glucose 0.50-0.80	No germs

Three increasingly severe stages of tuberculous meningitis may be described on the basis of clinically evident disorders. In stage 1, there is no impairment of consciousness, and neurological signs are absent or mild and local. In stage 2, consciousness is impaired, but there is neither deliriousness nor coma, with minor or moderately serious neurological signs such as paraparesia, hemiparesia, damaged cranial nerves. In stage 3, patients are delirious or in a coma, and always suffer from neurological conditions, sometimes severe, such as quadriplegia, stiffness, permanent contracture.

A recent review of cases observed in the last 15 years in Hong Kong shows the prognosis of tuberculous meningitis to be closely

linked to the stage at which it is diagnosed, irrespective of the duration and character of the chemotherapy administered.

Table 10

Outcome of treatment of tuberculosis in children in Hong-Kong, depending on the initial stage of the disease

Stages	Analysable cases	Complete recovery (%)	Functional sequelae (%)			Death (%)
			mild	moderate	severe	
I	49	96	2	2	–	–
II	78	78	9	8	4	1
III	72	21	5	25	32	17
Total	199	62	6	13	13	6

Taken from : HUMPHRIES M.J., TOEH R., LAN J., GABRIEL M. Factors of prognostic significance in chinese children with tuberculosis meningitis. Tubercle ; 1990, 71 : 161-168.

ACUTE MILIARY TUBERCULOSIS

Acute miliary tuberculosis occurs within weeks of primary infection, and often even before hypersensitivity to tuberculin develops. It usually takes the form of a systemic disease, with steady high fever (temperature of 39-40°C) and torpor. The pulse is rapid, there are digestive signs such as nausea, vomiting and diarrhoea, but no pinkish patches on the abdomen and no enlarged spleen, thus eliminating the possibility of typhoid fever. Respiratory signs - dyspnoea, cyanosis and occasionally respiratory distress - are consistently present.

Diagnosis is based on a full-face chest x-ray (the quality of which must be excellent), showing small, rounded, dense, micronodular shadows measuring 1 to 2 mm in diameter, dot-like or shaped like millet (whence the name of the disease). These micronodules are evenly spread over the entire expanse of both lungs, and are therefore more visible (and appear to be more numerous) on the lower two thirds of both areas, because of the thickness of the pulmonary parenchyma at that level. These main lesions are occasionally combined with other radiologically evidenced lesions such as primary infection-related hilar lymphadenopathy, confluent nodules and occasional slight cavitation or emphysemic bullae, which may result in mechanical pneumothorax or mediastinal emphysema, and increase dyspnoea.

In children, the micronodules are systematically disseminated throughout the organism. There are clinical indications of this : meningitis, above all, but also uni- or bilateral pleurisy, ascitis, pericarditis, regional lymphadenopathies, hepato-splenomegalia and in some few cases, blood conditions (leukemoid reaction, or conversely, medullar aplasia). Even when the disease is not clinically evident, screening for it is necessary, with investigations conditioned by the existence of clinical signs and the availability of test procedures.

Two tests are mandatory :

Fundus of the eye

- examination of the fundus of the eye usually shows choroidal tubercles (in over 50 % of cases) ;

Lumbar puncture

- lumbar puncture identifies any associated meningeal involvement, which determines the prognosis.

Other tests are only performed when presenting clinical signs are evidenced :

- culture of gastric lavage material to identify the bacillus (this may be preferred to direct microscopy), especially in the presence of confluent miliary damage or cavitation, or of fistulous mediastinal lymphadenopathy ;

- identification of the tubercle bacillus in the urine, by direct microscopy or culture following centrifugation of urine, may be positive in case of pyuria ;

- pleural puncture/biopsy uncovers sub-pleural tuberculous follicles in case of pleurisy ;

- investigation of the heart (clinical, electric and above all echocardiographic) identifies any pericarditis ;

- laparoscopy visualizes any peritoneal granulations ; in case of silent ascitis, a liver biopsy uncovers tuberculous follicles, and when the liver is enlarged it may show granulations on the peritoneum or liver ;

- culture of the product of bone marrow puncture (at the wing of the ilium) may point to medullar damage in the rare haematological manifestations.

Other complementary tests include a tuberculin test which, when positive, is a good presumptive argument whereas a negative result does not rule out a diagnosis of acute miliary tuberculosis. Blood tests show the absence of hyperleukocytosis, which rules out septicaemia and above all, acute staphylococcic miliary disease, most uncommon.

When untreated, acute miliary tuberculosis develops into severe pulmonary tuberculosis because of the excavation of confluent lesions and increasing respiratory failure. When associated with meningitis, the immediate vital prognosis and long-term functional prognosis are in direct relation to the precociousness of the diagnosis of meningitis and the child's age.

POST-PRIMARY RESPIRATORY TUBERCULOSIS

Post-primary pleural or pulmonary respiratory tuberculosis tends to occur in older children, around puberty, rather than in young children.

PLEURAL TUBERCULOSIS

Pleural tuberculosis is rare in children under 5. It usually occurs about 6 months after primary infection : 5 to 10 % of primary-infected children develop this complication. It is marked by asthenia, weight loss, a dry cough, pain in the side, and the existence of a pleural effusion syndrome (dullness,...) confirmed by a chest x-ray.

Pleural puncture finds a Rivalta-positive, sero-fibrinous fluid, rich in lymphocytes and in albumin (over 30 g/l). The tubercle bacillus

is identified in about 20 % of cases when the pleural fluid is cultured. Following evacuation of the pleural fluid, a second chest x-ray must be made to detect any underlying pulmonary or mediastinal damage (miliary, nodules, cavitation, segmental densities or mediastinal lymphadenopathy).

In older children, the tuberculous nature of the effusion may be proved when pleural biopsy using Abrams' needle is feasible, by histological examination of a pleural fragment (this procedure is more rapid and more reliable than culture).

For routine detection, however, the clinical context and evolution, a positive tuberculin test and pleural lymphocytosis with a positive Rivalta reaction suffice for a presumptive diagnosis of tuberculous pleurisy in a country where tuberculosis is highly prevalent, even in the absence of evidence of direct family contact with a source of infection.

PULMONARY TUBERCULOSIS

The frequency of pulmonary tuberculosis depends on the age at which primary infection with pulmonary tuberculosis took place. It occurs in about 4 % of children infected during infancy, and tends to develop several years later, in adolescence. Conversely, it is observed more frequently, in about 10 % of cases, in recently infected older children, usually one or two years after primary infection.

It is evidenced by the customary signs of tuberculosis : that is, moderate fever, especially in the evening, asthenia, loss of appetite, weight loss, as well as a pain in the side of the chest, a dry cough, occasionally producing sputum and even blood.

A chest x-ray shows :

Non-cavitary forms

- non-cavitary forms characterized by local nodules, occasionally in clusters located in the apical or subclavicular regions, clustered shadows ("infiltration") occasionally studded with denser nodules, rather infrequent lobar densities ("cheesy pneumonia") ;

Cavitary forms

- cavitary forms, characterized by the presence of typical pulmonary cavitation, a rounded clear spot with a 2 mm ring, connected to the hilus by the opaque streaks of a draining bronchus. These are occasionally quite extensive, when they are the result of the liquefying of cheesy pneumonia, with subsequent emptying of the lobe. Cavitary pictures are generally associated with nodular densities. If the case remains active for more than six months, there may be massive destruction of the pulmonary parenchyma, along with signs of fibrous stricture, affecting the mediastinum, the pleura and the diaphragm.

The pulmonary localization of tuberculosis, with or without cavitation, may be associated with other respiratory localizations, either pleural (in pleuropulmonary forms), mediastinal lymph nodes (the mediastino-pulmonary form) or complex (the mediastino-pleuro-pulmonary form).

Pulmonary tuberculosis is confirmed when tubercle bacilli are found in the sputa (collected by expectoration upon awakening, or after gastric lavage on an empty stomach on three consecutive

days), occasionally by direct microscopy and mostly by culture.

In cavitary forms, the bacillus is seen in over 80 % of cases ; in non-cavitary forms it may be found in over 50 % of cases provided the examination is repeated on several specimens collected before any treatment is given.

When bacteriological tests are negative, tuberculosis is diagnosed on the basis of a collection of presumptive evidence : the existence of a household source of infection, a positive tuberculin test, the clinical context and course, suggestive x-rays. Blood tests showing the absence of hyperleukocytosis and polynucleosis rule out bacterial infection with a single focus (pneumonia) or disseminated foci (pleuropulmonary staphylococcia, in particular).

EXTRA-RESPIRATORY TUBERCULOSIS

Haematogenous dissemination of the bacillus from primary infection lesions also has other, more or less belated consequences : these are other, extra-respiratory types of tuberculosis, mostly located in the regional lymph nodes, bones and joints, serous membranes and urogenital tract.

TUBERCULOSIS OF THE REGIONAL LYMPH NODES

This is by far the most frequent extra-pulmonary localization of the disease (about 50 % of extra-pulmonary cases of tuberculosis). It occurs within a few years of primary infection. Lymphadenopathies are usually cervical (more rarely axillary or inguinal). These are firm and resilient, with a diameter exceeding 2 mm, painless, and do not adhere to the skin, nor to the deeper layers, at the onset. Several months later they are surrounded by an inflammation (periadenitis) which adheres to the wall, they soften, become fistulous, and release a cheesy pus found to contain bacilli, when cultured. They may heal spontaneously in a matter of months or years, leaving burgeoning or retractile scar tissue (scrofula).

It may be confirmed before fistulization by puncture (presence of caseum) or by lymph node biopsy (discovery of specific follicular lesions). Following fistulization, diagnosis may be based on bacteriological examination of the pus.

The clinical characteristics and course of lymphadenopathies, a positive tuberculin test and normal haemogramme are usually sufficiently eloquent presumptive evidence of the disease, and rule out chronic lymphadenopathy caused by blood diseases (leukaemia, Hodgkin's disease).

OSTEO-ARTICULAR TUBERCULOSIS

Osteo-articular tuberculosis is the next most frequent extra-respiratory form of tuberculosis, after the lymph node localization. It too occurs in children within a few years of primary infection.

Tuberculosis of the spinal column

Tuberculosis of the spinal column (Pott's disease) is marked by pain in the spine, gibbosity, difficulty in walking. It may be complicated by paravertebral abscesses and paraplegia caused by medullar pressure.

Diagnosis is based on x-raying of the vertebrae, showing incipient pinching of the intervertebral disks, and later on, destruction of the vertebrae themselves or spindle-like paravertebral shadows indicative of cold abscesses. Clinical/radiological diagnosis is furthered by the clinical course, a positive tuberculin test and cyto-

bacteriological examination of pus from abscesses when these may be punctured.

Tuberculosis of the joints

Tuberculosis of the joints (usually of the knees or shoulders, "white swelling", "coxalgia" of the hips, or of the small articulations of the hands) causes chronic, non-inflammatory arthritis, with articulations deformed by inflammatory, and subsequently purulent synovial effusion produced by metaphyseal bony lesions (visible on x-rays). The resulting functional disability is attended by amyotrophy of the muscles located on either side of the articulation. Here again, clinical/radiological diagnosis is helped by the clinical course, a positive tuberculin test and synovial biopsy (or the cytobacteriological examination of intra-articular pus).

Tuberculosis of the long limb bones or of the flat bones (skull or ribs) is uncommon. For many years it was confused with chronic osteomyelitis caused by staphylococci. A positive tuberculin test and a normal haemogramme are only presumptive elements of diagnosis. Histological diagnosis of tuberculosis may be attained by biopsy of the bone, or of the trajectory of a cutaneous fistula.

TUBERCULOSIS OF SEROUS MEMBRANES OTHER THAN THE PLEURA

Pericarditis is rare in children. The ascitic form of peritonitis is relatively frequent on the other hand, especially in 10 to 14 year-old girls. Forms confined to the pelvis (pelvic peritonitis) may cause sterility by tubal obstruction).

URINARY TUBERCULOSIS AND OTHER LOCALIZATIONS

Tuberculosis of the kidney, like genital tuberculosis (epididymo-testicular tuberculosis in boys), is exceptional in children, including older children. Not only are such localizations unusual, but above all they occur very late, usually some 15 to 20 years after primary infection.

Other rare localizations of tuberculosis in children include tuberculosis of the liver, intestinal tuberculosis (affecting the mesenteric lymph nodes), tuberculosis of the skin, the brain and the nervous system.

Such rare localizations are also particularly difficult to diagnose, and require use of specialized investigatory techniques.

Diagnosis of tuberculosis in children is usually based on presumptive elements : the clinical picture and course, x-rays, a tuberculin test and biological testing, as well as on definite proof, either bacteriological or pathologico-anatomical.

For this reason, criteria for the diagnosis of tuberculosis in children, for use in national tuberculosis control programmes, must be strictly specified in documents (such as technical guidelines) so as to help physicians to label the cases they notify as appropriately and objectively as possible.

HOUSEHOLD CASE-FINDING FOR TUBERCULOSIS

• Identification of contacts

When an adult patient suffering from smear-positive pulmonary tuberculosis (or with negative microscopy and positive culture) is identified, personnel should always :

- record his/her recent, usual address and the exact address of the family (if possible, the address of the elementary school attended by his/her children) ;

- make a complete list of all people (children and adults) in household contact with him/her, living under the same roof, sharing meals and sleeping in the same place. Consulting the patient's family record book is not enough, since there may be elderly parents, unmarried brothers and sisters, or occasionally, married ones with children, other relatives, distant cousins or acquaintances living in the same household.

For this reason, the patient's answers to questioning should be completed by a visit to his/her home, so as to achieve an accurate list of people actually living in contact with the source of infection, their age and sex, as well as their kinship relation with the patient. The latter should be informed in advance of the home visit, which should be tactfully prepared. It is preferable that it takes place late in the day, when everyone is gathered at home and the head of the household is present.

Following the visit, each person living in contact with the patient is given written notification of an appointment for a free examination at the clinic (or at the nearest health unit). The appointment - day and time - must be convenient (it depends on when the clinic is open, and on the work or school schedules of the different family members), especially in the case of young children, who must be accompanied. Special attention must be given to children under 15, to make sure that they are all examined within two months of diagnosis of the source of infection.

• Case-finding in contact children

Children under 15 listed as contact subjects should be given an appointment at the clinic no more than one week after they are sent notification. If they do not come for their appointment, they should be seen during a second home visit, as soon as possible.

In both cases, a health worker questions the children or their parents, so as to decide which cases must be seen by a doctor or a medical assistant.

The following questions should be asked :

- does the child have fever? How much and since when?

- has he/she lost weight? How many kilos and how fast?

- does he/she vomit? Have headaches?

- does he/she cough? Have laboured breathing? If so, since when?

During the examination, the visiting nurse or medical assistant :

- checks for any swelling of the lymph nodes in the neck and armpits ;

- makes sure the arms, hands and fingers move freely ;

- makes sure there is no limping or gibbosity ;

- makes sure that the lower limbs and spinal column are mobile and flexible ;

- notes the volume of the abdomen.

At the end of the examination, the visiting nurse or medical assistant :

- records the child's age, weight and height on the family card, across from his or her name ;

- notes whether a BCG vaccinal scar is present ;

- performs a tuberculin test ;

- makes an appointment with the child for 3 full days (72 hours) later, at the clinic.

If the child has fever, vomiting, a persistant cough, weight loss or any other abnormal sign, he/she must be referred immediately to the doctor, and is therefore given an appointment at the clinic for the following day.

For the other children, the decision is guided by the outcome of the examination by the nurse or medical assistant, along with the result of the tuberculin test, and is made 3 days after performance of the tuberculin test, when it is read.

If the child has no abnormal sign, has one (or several) BCG vaccinal scars (corroborated in some cases by his/her immunization record book kept by his/her mother) and is tuberculin-positive, the child (or the parents) are told that he/she is protected by the BCG vaccination and should come (or be brought) to the clinic again if any symptoms develop. No x-ray is needed.

If the child does not show any abnormal sign, has no vaccinal scar and is tuberculin-negative, a chest x-ray should be done and the doctor's advice sollicited before proceeding with BCG vaccination or a second tuberculin test.

This strategy results in the identification of four groups of children :

- those who may be diseased, because they have abnormal symptoms : they should be referred to the doctor for diagnosis and when needed, a decision as to curative chemotherapy. This is the smallest group ;

- those who have been infected recently, are not BCG-vaccinated, but have no symptom and should be shown to the doctor for the prescription of preventive chemotherapy ;

- those who are neither infected nor BCG-vaccinated, and should be immunized, using the BCG, as soon as possible ;

- those who are BCG-vaccinated, are apparently healthy and may be sent home.

THE STANDARDIZED TUBERCULIN TEST

The standardized tuberculin test recommended by WHO is based on the intradermal injection of a known amount of purified tuberculin. This is the preferred method for exploring children's reaction to tuberculin.

• Required equipment

- a short (1 cm), fine (5/10) intradermal needle with a short bevel ;

- a syringe, with special, 0.01 ml graduations, with a plunger made leakproof by a rubber or plastic ring at one end (such as the Omega-Microstat syringes, or the single-use, disposable tuberculin syringes), or with a long metal plunger (such as the Fortuna WG Co tuberculin syringes). Use of the usual hypodermic needles, whose plunger is not necessarily leakproof, or of Barthélémy syringes, which occasionally only show graduations in insulin units, should be proscribed.

• Tuberculin

Purified tuberculin is used. The two kinds most frequently used in Africa are :

- tuberculin from the Statens Serum-Institut of Copenhagen, which is a PPD-RT 23 tuberculin (PPD = purified protein derivative), to which Tween 80 is added. It exists in liquid form, requires refrigeration, has a red label and was sold for 7 francs (US$ 1.40) the milliliter - or 0.7 francs (14 cents) per child - in Paris in June 1991, to which some wastage must be added. Moreover, a considerable price rise is expected in 1992.

The intradermal injection of 0.1 ml of this solution corresponds to 2 international units of tuberculin RT 23.

- Pasteur tuberculin, which is a purified tuberculin packaged in boxes of ampoules containing lyophilized purified tuberculin, and 1 ml of solvent. Lyophilized tuberculin is a white powder which must be reconstituted before use. To do so, all of the powder must be brought to the bottom of the ampoule by gently tapping the sides before it is opened ; once the ampoule containing all of the dried powder is opened, the contents of the solvent ampoule is poured into it. To make sure the powder is properly dissolved, the liquid is pumped in and out of the syringe twice before use.

The intradermal injection of 0.1 ml of the reconstituted solution corresponds to 10 units of tuberculin IP48 and is the same as the injection of 2 units of tuberculin RT23.

It is unnecessary to administer more than 2 units of PPD RT23 tuberculin or 10 units of PPD IP48 tuberculin to achieve a tuberculin reaction.

• Intradermal injection of tuberculin

Following simple cleaning of the skin using alcohol, ether or hydrogen peroxide, the injection is administered to the skin of the anterior side of the forearm, at some distance from the BCG or other scars, one third up and two thirds down the child's forearm. The person performing the test grips the child's forearm firmly with one hand, so as to hold the skin taut, then administers the injection with the other hand, by thrusting the needle into the derma, at an angle. As soon as the upper end of the bevel has disappeared into the skin, the tuberculin is injected slowly, taking care to watch the piston move from one graduation to the next, to be sure that the amount of tuberculin injected is exactly 0.1 ml.

If the needle is properly inserted in the derma, it encounters an elastic resistance to the injection, and causes a white, raised dermal wheal to occur around the point of the needle, with pronounced pits corresponding to the roots of hair (giving the wheal an "orange peel" look). If no such wheal develops and there is no resistance to the injection, then the needle is not inserted properly: it should be removed and the operation repeated.

Remember ! To inject 0.1 ml of tuberculin, it is the descent of the plunger in the syringe that must be watched, and not the size of the wheal.

• Reading of the tuberculin test

The tuberculin test is read 3 full days (72 hours) after the injection : for instance, if the injection took place on Monday at 10 A.M., the test should be read on the following Thursday at 10 A.M.

First the appearance and colour of the skin at the injection site are noted : the skin may be normal, or slightly raised by an induration with a more or less reddish centre, or again, there may be a raised induration surrounded by a large red areola, occasionally with a few blisters on it.

To measure the test result, the induration is felt with the pulp of the index finger, to determine its edges, which may be steep, using a fine-point marker pen, and its transverse diameter is measured using a transparent measuring stick with millimeter graduations. The test result is always recorded in millimeters.

When blisters are present on the induration, the fact should be mentioned in addition to the test result expressed in millimeters.

Remember ! It is the transverse diameter of the induration and not its vertical diameter, nor the diameter of the red areola surrounding the induration that is measured. The results are expressed in millimeters and not qualitatively : results expressed as "positive" or "negative", or using crosses (+, ++, +++) must be rejected. An induration with a diameter of five millimeters or more is indicative of a positive reaction.

A SATISFACTORY CHEST X-RAY

A high-quality full-front chest x-ray is absolutely necessary for the diagnosis of respiratory tuberculosis in a child.

• Technical precautions

Some technical precautions must be taken. Exposure time should be as short as possible, not exceeding 1/100th of a second. This requires a satisfactory amperage, of 200 to 500 mA.

For a normal x-ray, a voltage of between 50 and 80 kV is used. However, if mediastinal opacities are to be analysed accurately and kinetic blur decreased, it may be worth while to request a high voltage x-ray, between 100 and 150 kV, provided a diaphragm is used.

There must be a distance of at least 1 m 20 between the light and the film.

The child's respiratory movements must be watched.

The picture should be taken at the beginning of an expiration, just at the end of an inspiration. In older children, an experienced worker easily obtains pictures of deep inspiration. In infants, chest pictures must be taken at the beginning of crying.

In older children, the full front picture is taken at a postero-anterior angle, standing up, with the child's belly turned toward the plate. For young children the antero-posterior angle is preferable, with the child in a semi-reclining position, back turned toward the plate. Infants are x-rayed lying down.

• Judging quality

Make sure the picture is properly centred, that the visible volume of the pulmonary parenchyma is sufficient, and that penetration is neither excessive nor insufficient.

It is important that the picture be well centred. The internal edge of both clavicles must be equidistant from the axis of the spinous processes, the pleural culs-de-sac and the apexes must be in the picture, the shoulderblades must be out of the way, and not cover the pulmonary parenchyma. The pulmonary volume must be sufficient ; this means that the shadow projected by the diaphragmatic dome should not be seen above the 6th intercostal space. If the picture is properly taken at the end of an inspiration, the dome of the diaphragm is seen in the 8th intercostal space.

The quality of penetration is determined by studying the soft tissues and the spinal column. The spinous processes should be visible down to D4, and masked by the cardio-aortic shadow below D4.

REMEMBER ! NEVER INTERPRET A CHEST X-RAY IF :
- ITS QUALITY IS POOR
- IT IS NOT IDENTIFIED
- IT IS NOT DATED.

SCORING SYSTEMS FOR DIAGNOSING TUBERCULOSIS

The diagnosis of tuberculosis in children usually rests on a series of facts : clinical and radiological signs, the existence of close or recent contact with a source of infection and the results of a tuberculin test (the value of which is questionable when BCG vaccination has been performed). Confirmed diagnosis, based on bacteriology or pathological histology, is actually rarely established before treatment is implemented. For this reason several authors have suggested scoring systems for the establishment of a reasonably probable diagnosis of tuberculosis in children, on the basis of a point system. These have been experimented and recommended in Chile (1) and India (2,3). Some have been applied in Asia, in a locally modified form.

Actually, the variable assessment of the different points contributing to the score constitutes a considerable source of biases. Depending on whether 7 points are assigned to elements confirming diagnosis (bacteriological or pathological-anatomical proof), or only 3, the points given to the other parts of the score are more or less decisive. Further, the interpretation of recent, segmental densities, of lasting segmental densities and atelectasies, as well as of mediastinal or hilar lymphadenopathies remains highly subjective : it depends both on the quality of the chest x-ray and on how experienced the reader is.

Last, the epidemiological context and the extent of application of BCG vaccination in different countries variously affects the number of points assigned by the authors to a positive tuberculin test at each age and for each induration size (often measured quite subjectively !).

In conclusion, while the scoring system may be found useful in epidemiological surveys, as an accessory for trained workers (who collect their own data, using stable techniques) in the analysis of homogeneously observed facts, it should not be used routinely in the application of antituberculosis programmes.

It is preferable to teach doctors (and medical students) to apply strict diagnostic criteria for each form of childhood tuberculosis, so as to help them learn proper classification and notification of cases of tuberculosis in children.

(1) STEGEN G., JONES K., KAPLAN P. Criteria for guidance in the diagnosis of Tuberculosis. Pediatrics. 1969 ; 43, 2 : 260-263.

(2) MADHAYACHANDRAN NAIR P., PHILIP E.A. Scoring system for the diagnosis of tuberculosis in children. Indian Pediatrics. 1981 ; 18 : 299-303.

(3) UDANI P.M. Scoring technique in the diagnosis of tuberculosis in children. In WHO/IUATLD/-JSG/BP document, 1981.

CRITERIA FOR DIAGNOSING TUBERCULOSIS IN CHILDREN

Category	Criteria
Primary infection	Radiology : primary complex. Tuberculin test : induration always over 6 mm wide (after local complications : culturing of positive sputa).
Tuberculous meningitis	Meningeal syndrome with occasional paralysis of the ocular nerves. Radiology : occasional miliary or primary complex. CSF : lymphocytosis, hypoglycorrhachia, hyperalbuminorrhachia.
Miliary tuberculosis	Dyspnoea. Radiology : typical picture. F.E. choroidal tubercles with signs of dissemination : meningitis, etc.
Post-primary pulmonary tuberculosis	Clinical signs. Radiology : nodules and/or cavitation. Bacteriology : presence of TB in sputa (microscopy and/or culture).
Pleural tuberculosis	Subacute lymphocytic serofibrinous pleurisy. Tuberculin test : induration over 6 mm wide. Pleural biopsy : tuberculous follicle (occasionally)
Other extra-respiratory forms	Suggestive clinical and/or x-ray picture. Tuberculin test : induration over 6 mm across. Cyto-histological analysis of lesions or bacteriological examination of pus (when feasible).

BACTERIOLOGICAL DIAGNOSIS OF TUBERCULOSIS IN CHILDREN*

Most cases of tuberculosis in children involve extra-pulmonary disease or primary infection in which bacilli are not easy to isolate. Even in cases of pulmonary tuberculosis, bacteriological diagnosis is delicate, since the child does not expectorate much and lesions generally affect the lymph nodes. When the child is over twelve and shows cavitary pulmonary damage, bacteriological diagnosis is relatively easy. Last, in some cases of extra-pulmonary tuberculosis in which puncture (of the meninges, pleura, lymphadenopathies or superficial abscesses) or the collection of contaminated fluids (urine) is feasible, culture may reveal the presence of bacilli.

Bacteriological diagnosis of respiratory tuberculosis in children

Localization	Total number of cases	Bacteriologically confirmed cases			
		Total		by microscopy (%)	by culture only (%)
		No.	%		
Mediastinal (primary infection)	525	46	8.8	—	4
Pulmonary no cavitation	174	72	41	16	25
Pulmonary with cavitation	134	106	79	55	24
Pleural	127	20	16	—	16

Source : ANANE T. Personal study, 1991.

In those cases where bacteriological diagnosis of childhood tuberculosis is possible, then, it usually comes late, and the decision to treat must be made before the laboratory results arrive. However, in cases of pulmonary tuberculosis and in certain cases of extra-pulmonary tuberculosis, the bacillus may be identified by direct microscopy and above all, by culture, provided some technical requirements are respected during specimen-taking, transport and handling of specimens in the laboratory (1, 2, 3, 4).

*** By Safia KHALED.**

(1) GROSSET G., GROSSET C., TRUFFOT-PERNOT Ch. The bacteriology of tuberculosis: the role of the laboratory in the diagnosis and treatment of tuberculosis. Bull. Int. Un. Tuberc. 1982 ; 57/3-4: 226-233.

(2) Technical guide for sputum examination for tuberculosis by direct microscopy. Bull. Int. Un. Tuberc. 1978 ; supplément n° 2.

(3) KUBICA G.P. Correlation of acid-fast staining methods with culture results for mycobacteria. Bull. Int. Un. Tuberc. 1980 ; 55/3-4 : 117-124.

(4) PARROT R., GROSSET J. et al. Le rôle et la place des informations bactériologiques dans l'identification des sources de contagion. Rev. Fr. Mal. Resp. 1976 ; 4 : 289-304.

Specimen-taking

In cases of pulmonary tuberculosis, it is often necessary to resort to collecting secretions swallowed during sleep, using gastric lavage, or secretions coming from the bronchi following an effort at coughing, using laryngeal swabs, since children are often incapable of intentional expectoration.

For gastric lavage, the equipment used is a disposable polypropylene nasal probe and a sterile 20 ml syringe. The operation must be done on an empty stomach : the child is asked to breathe calmly, while the probe is gently introduced through the nose. Once it is definitely in the gastric cavity, a sufficient amount (5 to 10 ml) of gastric fluid is withdrawn, using the syringe. The content of the syringe is then poured into a sterile, screw-top tube. Specimens are taken on three consecutive days.

Following use, the glass syringe is immediately dipped in chlorine solution, then washed and sterilized in dry heat, for reuse. If disposable syringes are available, the specimen may be sent directly to the laboratory in the syringe provided it is well stoppered.

The equipment for laryngeal swabs is comprised of an absorbent cotton swab mounted on a straight stick and placed in a closed glass tube, all of which is sterilized at 160°C for 20 minutes. Sterile ready-to-use swabs may also be used when they are sold locally.

The specimen is taken in the morning, on an empty stomach, before any food is eaten. The child is seated, with his/her head leaning back, mouth open, and is asked to hold his/her tongue, using a compress. The swab is dipped in physiological saline solution, then put into the mouth, between the tonsils, as deep down as possible, without touching the pharyngeal walls or the base of the tongue. The child is asked to cough, and when he/she has done so two or three times the swab is removed and placed in the sterile tube with no further handling.

Workers are exposed to a serious risk of contamination when taking bronchial mucous specimens during induced coughing, and must therefore be protected against the droplets of mucous by a mask or a transparent screen, and wear gloves and a coat specially reserved for this use.

In cases of extra-pulmonary tuberculosis, specimens may come from open lesions (abscesses, fistulas, urine), which are necessarily contaminated by common flora. These specimens contain many germs, and must be handled and treated like sputum. Conversely, when the lesions are closed (pleural or cerebrospinal fluid, pus from a non-fistulous abscess), the chances are that specimens contain a single germ only : strict asepsis must then be respected when handling them, so that culturing of the specimen may be done directly at the laboratory, with no prior treatment. Culturing of some fluids such as cerebrospinal or pleural fluid may be done directly at the patient's bedside, using the puncture needle. Surgical biopsy material must be placed in a sterile container containing physiological saline solution.

Transportation and storage of specimens

All specimens must be clearly identified and labelled. A record card mentioning the patient's identity, the nature and date of the specimen, the localization of the lesion, past history of antituberculosis treatment of the patient and/or of the contact person identified as diseased must necessarily accompany the specimen itself.

If specimens must travel a long way to the laboratory, satisfactory transportation must be ensured. This means that bottles containing the specimens are hermetically sealed and packed in a hard box (made of wood or metal) which is easy to clean and chlorinate:

this protects them from shock during transportation. The record cards are placed in an envelope which is given directly to the agent in charge of transferring the specimens.

If there is any delay in forwarding specimens, they may reasonably safely be stored in a refrigerator at + 4°C for 6 to 10 days.

Laboratory work on specimens

Microscopy is a major diagnostic and epidemiological tool ; for this reason it should be performed with great care.

Smears are made using a purulent particle, spread thinly on a slide over a surface measuring 2 cm long by 1 cm wide. After fixation, the smear is stained. The staining method - be it Ziehl-Neelsen staining or auramine (for use in fluorescence) - is based on the stainability of mycobacteria : in other words, the fact that they are acid-fast, and therefore able to retain a colour despite the combined action of acid and alcohol. These methods involve three phases, then : staining, then decolourization using acid and alcohol, and last, counter-staining to enhance the contrast. Fluorescence-stained smears may be read sooner, but this process requires a fluorescent microscope, which is more expensive than one using white light.

Reading of smears must be standardized, by travelling along the smear lengthwise, considering that each 2 cm of smear represents 100 microscopic fields. The findings are expressed quantitatively :

- by the number of bacilli per field when the slide is rich (over 10 AFB/field) (AFB = acid-fast bacilli) ;

- by the number of bacilli per 100 fields when the slide is moderately rich (that is, between 1 and 9 AFB/field) ;

- by the number of bacilli per 300 fields when few bacilli are present (less than 1 AFB/field).

Workers should be aware that microscopy is more often positive in cavitary lesions than in the primary infection or lymph node lesions which are frequently encountered in children. Culture may be more profitable in the latter cases, but it should be clear that culturing of bacilli requires adequate facilities, a serious investment in laboratory equipment (hood, centrifuge, agitator, incubator), and trained personnel.

When multiple-germ specimens are cultured in order to isolate the tubercle bacillus, prior decontamination is required to remove common germs, which proliferate more rapidly than M. Tuberculosis. This is done by treating the specimen with a detergent or an antiseptic such as sodium hydroxide (4 % NaOH) : commensal bacteria are destroyed while the viability of the bacilli is not overly threatened. However, when few bacilli are present, care must be taken to avoid drastic decontamination which may destroy some of the mycobacteria and thus decrease the sensitivity of culturing. The quality of decontamination may be checked by evaluating the percentage of cultured specimens lost through environmental soiling. The percentage of such soiled cultures should be between 2 and 3 % : when below 2 %, decontamination is too strong, and when over 3 %, decontamination is inadequate.

The usual decontamination procedure using sodium hydroxide and centrifugation is as follows : for one volume of specimen, add 2 volumes of 4 % NaOH. The mixture is shaken up for 15 minutes then centrifuged at 3,000 rotations/minute for 15 minutes. The

supernatant is discarded in a container of chlorine and replaced by the same volume of sterile distilled water. Shake for 15 minutes, centrifuge, remove the supernatant, discard it in chlorine solution and culture the remainder on a Loewenstein-Jensen medium, using 4 to 6 drops per tube and 4 tubes per specimen. Incubate at 37°C in a controlled-temperature incubator (M. Tuberculosis is killed at 39°C).

Uncontaminated presumably single-germ specimens are cultured on Loewenstein-Jensen medium with no prior treatment. In the case of fluids (cerebrospinal or pleural fluid), the entire specimen is cultured, within the limits set by the amount of medium available.

Cultures are read after 28 days of incubation : the culture is positive when rough, cream to beige-coloured colonies with a diameter of 2 to 3 mm are seen. The results are expressed quantitatively as the number of colonies per tube. If the culture is negative on the 28th day, incubation is pursued until the 42nd day : then again, negative cultures are retained until the 72nd day. At that point they may be considered definitely negative.

The purpose of identification of colonies is to make sure that the tuberculosis bacillus is effectively involved. Identification is based on the colony's appearance, and on whether it is acid-fast, as shown by Ziehl-Neelsen staining of a smear containing the colonies. Identification of the species is based on a series of biochemical tests : catalysis, NO^3 nitrates reduction, production of niacin and resistance to TCH (thiophene carboxylic acid). The catalytic activity of M. Tuberculosis is heat-labile, it reduces nitrates, resists TCH and produces large amounts of nicotinic acid.

Isolation of the strain in culture is a preliminary to testing for sensitivity to antibiotics. The value of sensitivity tests is more epidemiological than therapeutic (treatment regimens are standardized). They make it possible to evaluate bacterial resistance (primary and acquired) in children, and are indicative of the effectiveness of both treatment and management of patients.

Tests for identifying mycobacteria and sensitivity of the tubercle bacillus to antibiotics are difficult to administer and to interpret : for this reason they are only done in central reference laboratories at the national level.

New laboratory techniques

New, more rapid and more sensitive techniques for confirming diagnosis of tuberculosis are currently being developed. Some of these enable the early detection of growth of M. Tuberculosis, while others identify the chemical components of the bacillus within specimens, so that antigens of the mycobacteria, or antibodies, may be sought. Last, molecular biology and genetic engineering techniques are potentially available. The value of these different techniques is variable. Their use by specialized laboratories depends on the advantages yielded in comparison with their inherent limits, in some cases, and with the constraints imposed by them (5).

Radiometric assay may be used for the early detection of the growth of Mycobacterium tuberculosis. This is a reliable method, provided any other bacteria contained in the specimens have been removed by decontamination. It does suffer from three major drawbacks, however : the cost of the equipment and of the medium, since the latter contains a radioactive substance (carbon 14) the manipulation of which involves strict constraints,

(5) GROSSET J., TRUFFOT-PERNOT Ch. Le diagnostic rapide de la tuberculose. Rev. Prat., Méd. Gén. ; 20 mai 1991, 5, 138.

and last, the availability of the marked product, which is to say its importation in developing countries.

In childhood tuberculosis, radiometric assay, like culture on a solid medium, may provide a posteriori confirmation of a diagnosis already established on the basis of presumptive evidence.

Use of biochemistry to detect M. Tuberculosis is feasible, since the walls of mycobacteria possess varying amounts of fatty acids (mycolic acids) depending on the species, and the profile of these may be determined. Practically speaking, this method is too diffuse and complicated to be appropriate for routine diagnosis.

Use of gaseous phase chromatography and mass spectrometry to detect tuberculostearic acid in pathological specimens is also a possibility. The presence of tuberculostearic acid is viewed as a reliable indicator of tuberculous infection ; this technique is just as sensitive as culturing, but is more rapid (8 hours of manipulation). Once again, the cost of the equipment and the need to handle sufficient numbers of specimens at once if it is to be profitable, along with the lack of standardization, make it relatively inappropriate under present circumstances.

Immunodiagnostic methods detect the tuberculosis antibody (serodiagnosis) or the antigen in the pathological specimen. Techniques for detecting the antigen/antibody reaction have progressed, and those now used routinely make use of enzyme markers (the ELISA test). Detection of the antigen in the pathological specimen requires identification of the target and availability of the specific antibody.

The predictive value of immunological testing is proportionate to the specificity of reagents and raises the question of their reliability.

Genetic engineering techniques may also be used for the detection of M. Tuberculosis. The DNA within the organism takes the shape of two strands spiralling around each other to form a double helix, and which may separate under the action of a high temperature, for instance. When the temperature drops, they come together again in a specific pattern (hybridation). This phenomenon is exploited for diagnostic purposes in DNA probe techniques and in genome amplification by polymerase chain reaction (PCR).

There is a need for a rapid, sensitive, reliable and inexpensive technique capable of confirming diagnosis of cases of tuberculosis in children. At present, no one technique meets all of these criteria at once while being susceptible of decentralization for use in intermediate level laboratories. However, PCR seems quite promising, but requires further standardization and simplification.

TREATMENT OF TUBERCULOSIS IN CHILDREN*

At present, the preferred treatment of different localizations of tuberculosis in children is a short course of chemotherapy. As in the treatment of tuberculosis in adults, the former chemotherapy regimens, which were given for 12 or 18 months, have been replaced by "short" courses, which never exceed eight months. These regimens are more effective than their earlier counterparts, because they associate at least three essential antituberculosis drugs - isoniazid, rifampicin and pyrazinamide - during the first two months of treatment.

Three major documents have guided this evolution : the recommendations of the Scientific Committees of the International Union against Tuberculosis and Lung Diseases (IUATLD) on chemotherapy regimens in tuberculosis, in 1987 (29) and on tuberculosis in children in 1990 (30), the guidelines of the WHO Tuberculosis Unit for the treatment of tuberculosis in adults and children, in 1991 (31).

The decision as to what short chemotherapy regimen to give children with tuberculosis (that is, the number of drugs necessarily associated during the initial phase of treatment, and the total duration of the latter : four, six or eight months) depends on three main factors :

- the amount of bacilli in the tuberculous lesions ; this depends on the localization of the disease ;

- the risk of failure of chemotherapy due to bacterial resistance to isoniazid and/or streptomycin ;

- the fact that the vital or functional prognosis of some extra-pulmonary localizations is particularly serious in children.

The key to recovery is the careful organization of care for children requiring treatment, in close collaboration with their family (and especially their mother).

CHOICE OF CHEMOTHERAPY REGIMENS

Tuberculosis chemotherapy regimens for children are not fundamentally different from those administered to adults within any given national programme.

However, the intermittent, supervised administration of drugs twice or three times a week is not advisable for children, for prac-

* By Pierre CHAULET, Mustapha-Saadi MAZOUNI and Nadia AIT KHALED.

(29) International Union against Tuberculosis and Lung Diseases. Antituberculosis regimens of chemotherapy. Recommendations from the Committee on Treatment of the IUATLD, Bull. Int. Un. Tuberc. 1988, 63, 2 : 60-64.

(30) A statement of the Scientific Committees of the IUATLD. Tuberculosis in children. Guidelines for diagnosis, prevention and treatment. Bull. Int. Un. Tuberc. 1991 ; 66, 1 : 61-67.

(31) Tuberculosis Unit, WHO, Geneva. Guidelines for tuberculosis treatment in adults and children in national tuberculosis programmes. WHO/TUB/91, 161.

tical reasons : in the rural parts of developing countries, this means that children must be brought to a clinic or health outpost by their mother or another adult twice or three times a week for several months ; furthermore, it is not easy to get small children to swallow the required number of tablets, necessarily higher during intermittent treatment than when they are taken daily.

Irrespective of the regimen chosen, it should be applied to all diseased children in a standardized fashion, on the basis of criteria specified in the technical guidelines of the national tuberculosis control programme.

In new cases of tuberculosis (children with no past history of treatment or treated for less than one month), two categories of chemotherapy regimens may be prescribed.

Regimens with four drugs lasting 6 to 8 months

The first includes six to eight month-long courses comprised of four drugs during the initial intensive treatment phase. These regimens are given in bacilli-rich forms when there is a non-negligeable risk of failure of treatment due to initial bacterial resistance, and in severe forms of pulmonary or extra-pulmonary disease.

The regimen of choice involves a daily dose of isoniazid plus rifampicin for six months, supplemented with a daily dose of pyrazinamide and streptomycin (or ethambutol) for the first two months.

An alternative regimen, practically as effective, is exactly the same for the first two months, during which isoniazid, rifampicin, pyrazinamide and streptomycin are taken daily, and is followed by a consolidation period (longer, since rifampicin is eliminated), lasting six months, during which an association of isoniazid and thiacetazone (or of isoniazid and ethambutol) is given. These regimens are equally effective in the treatment of pulmonary tuberculosis in patients with originally sensitive bacilli (the majority) and of patients with initially isoniazid-resistant bacilli ; the latter represent between 3 and 20 % of new cases of pulmonary tuberculosis, depending on the country.

Regimens with three drugs lasting 4 to 8 months

The second category involves four to eight-month courses with only three drugs during the initial treatment phase. These regimens are given in paucibacillary forms, which include the vast majority of cases of childhood tuberculosis and of extra-pulmonary tuberculosis. Streptomycin is not given during the initial phase.

The regimen of choice includes a daily combination of isoniazid and rifampicin for four months, supplemented with a daily dose of pyrazinamide during the first two months. If the lesions have not disappeared completely by the end of the fourth month (which is unusual), treatment may be pursued by isoniazid only until the end of the 8th month.

Alternative regimens eliminate rifampicin after the first two months: they must therefore necessarily be continued for eight months. After the initial two-month period, during which isoniazid, rifampicin and pyrazinamide are given daily, the consolidation phase, lasting six months, associates isoniazid and thiacetazone,

or sometimes isoniazid and ethambutol daily, or again isoniazid and ethambutol for two months followed by isoniazid only for the last four months (when finances prohibit the prescription of ethambutol for all patients for the entire six months).

Failure and relapse

The risk of bacterial resistance is higher in the rare cases of failure observed at the end of treatment, or of relapse following treatment, than in previously untreated patients. The main objective is coverage of this risk by the standardized chemotherapy regimen offering the best chances of effectiveness. For this reason an eight-month course composed of five drugs for the first two months should be applied. This course involves two phases :

- an initial three-month phase, with daily chemotherapy associating isoniazid, rifampicin, ethambutol and pyrazinamide, supplemented daily with streptomycin during the first two months ;

- a five-month consolidation phase combining three drugs : isoniazid, rifampicin and ethambutol daily until the end of the eighth month.

This regimen, rarely applied to children, effectively cures previously treated pulmonary tuberculosis patients, who tend more to have bacteria resistant to isoniazid and/or streptomycin than do untreated patients.

Table 11

Antituberculosis chemotherapy regimens applicable to children in the framework of national tuberculosis control programmes

	Regimens of choice		Alternative regimens	
	Duration (months)	Nature of chemotherapy*	Duration (months)	Nature of chemotherapy*
New cases				
1. abundant bacilli	6	2 SRH Z/4 RH 2 ERHZ/4 RH	8	2 SRH Z/6 TH 2 SRHZ/6 EH
2. few bacilli	4 8	2 RHZ/2 RH 2 RHZ/2 RH/4 H	8	2 RHZ/6 TH 2 RHZ/6 EH 2 RHZ/2 EH/4 H
Bacteriologically positive previously treated cases				
High risk of bacterial resistance	8	2 SRHEZ/1 RHEZ/5 RHE		

* The drugs used in chemotherapy regimens are conventionally represented by their usual abbreviations : H = isoniazid ; R = rifampicin ; Z = pyrazinamide ; S = streptomycin ; E = ethambutol ; T = thiacetazone.

The figure in front of each group of letters shows the number of months of the phase (initial or consolidation) during which drugs are administered once a day.

INDICATIONS FOR CHEMOTHERAPY REGIMENS

CHEMOTHERAPY WITH FOUR DRUGS LASTING 6 TO 8 MONTHS

Four-drug chemotherapy regimens lasting 6 or 8 months are recommended in bacteriologically positive forms of pulmonary tuberculosis, as well as in those forms of tuberculosis for which the vital or functional prognosis is poor. According to the guidelines recently set down by WHO (32), the indications for these regimens may be formulated as follows :

- recent pulmonary tuberculosis, smear-positive or with positive culture only ;

- pulmonary tuberculosis with extensive lung density, judged to be active, smear-negative ;

- primary tuberculosis with hilar or mediastinal lymphadenopathy and an apparently active pulmonary lesion, even in the absence of bacteriological confirmation, with or without associated pleurisy ;

- primary tuberculosis complicated by endobronchial glandular fistulization, with bacilli in the sputa ;

- acute miliary tuberculosis and tuberculous meningitis ;

- vertebral tuberculosis with neurological complications ;

- extensive tuberculosis of the serous membranes, the functional prognosis of which may be bad : double pleurisy, pericarditis, ascitic peritonitis, polyserositis ;

- tuberculosis of the kidney, exceptional in children.

WHO recommends that treatment combining isoniazid and rifampicin be prolonged to 8 or 9 months in cases of tuberculous meningitis or vertebral tuberculosis with neurological complications.

In tuberculous meningitis and tuberculosis of the serous membranes (and occasionally in miliary tuberculosis with acute dyspnoea), prednisone is added to the regimen for four to six weeks, at the initial dose of 1 mg/kg/day, with a gradual, weekly decrease of 5 mg a day thereafter.

CHEMOTHERAPY WITH THREE DRUGS LASTING 4 TO 8 MONTHS

Four or 8-month chemotherapy regimens composed of three drugs during their initial phase are indicated in all other forms of tuberculosis. According to the recent WHO guidelines, indications may be outlined as follows (33) :

- recent pulmonary tuberculosis with negative microscopy, with nodular lesions (densities measuring less than 5 mm across), limited in extent, covering a surface smaller than that of the upper right lobe, for instance ;

- primary tuberculosis with isolated hilar or mediastinal lymphadenopathy, no visible parenchymal damage, possibly with diffuse segmental or lobar density, indicative of a ventilation disorder caused by bronchial compression of lymphadenopathic origin ;

- most cases of extra-pulmonary tuberculosis in children, which are usually benign : unilateral pleurisy with slight or moderately

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(32) Ibid. 31.

(33) Ibid. 31.

copious effusion, tuberculosis of the regional lymph nodes, osteo-articular tuberculosis of the limbs, vertebral tuberculosis with no neurological complications, etc.

When extensive density develops in primary tuberculosis, and in slight or moderately abundant pleurisy, prednisone is added to the regimen for four to six weeks, at the initial dose of 1 mg/kg/day, with a gradual, weekly decrease of 5 mg a day thereafter.

For this second group of indications, which includes most forms of childhood tuberculosis, a four-month course (associating isoniazid and rifampicin during the first two months only) is usually adequate.

However, if the four-month course is given in a case of nodular pulmonary tuberculosis with lesions initially covering a surface seen on the chest x-ray to exceed 10 cm^2 on the pulmonary parenchyma, or if there are signs that extra-pulmonary lesions are active at the end of the 4th month (particularly in the regional lymph nodes), treatment should be continued until the end of the eighth month, using isoniazid only for the last four months.

CHEMOTHERAPY WITH FIVE DRUGS LASTING 8 MONTHS

The few children suffering from pulmonary tuberculosis who still discharge bacilli in their sputa after more than five months of chemotherapy, or who begin to expectorate bacilli again (at two different tests performed at an interval exceeding two weeks) within three years of termination of full treatment constitute failures or relapses, and acquired bacterial resistance to isoniazid and/or streptomycin should be suspected in these cases.

These are the only instances in which an eight-month course with a five-drug regimen during the initial phase is indicated.

If the evolution is satisfactory after twelve weeks, and conversion is achieved, the three-drug consolidation phase should be pursued to its conclusion. If an initial sensitivity test is available, and it proves that bacilli were still sensitive to isoniazid then, the entire consolidation phase may include an association of rifampicin and isoniazid, without ethambutol. If conversion is not achieved after twelve weeks, the four drugs administered during the third month should be continued until the end of the sixteenth week, and the three-drug treatment continued normally until the end. If the result of the initial sensitivity test indicates bacillary resistance to isoniazid and rifampicin, the chances of achieving lasting conversion and recovery are slight.

Table 12

Indications for chemotherapy regimens in childhood tuberculosis

Chemotherapy regimens	Indications
2 SRHZ / 4 RH or 2 SRHZ / 6TH	Pulmonary tuberculosis, smear-positive or with positive culture only. Massive pulmonary tuberculosis, smear-negative. Primary tuberculosis with lymphadenopathy and pulmonary density considered active or with fistulous bronchial lymphadenopathy. Acute miliary tuberculosis. Massive tuberculosis of the serous membranes : double pleurisy, peritonitis, pericarditis, polyserositis*.
2 SRHZ / 6 RH	Vertebral tuberculosis with neurological complications and tuberculous meningitis*.
2 RHZ / 2 RH or 2 SRHZ / 6 TH	Pulmonary tuberculosis, smear-negative and with limited nodular lesions. Pulmonary tuberculosis with isolated hilar/mediastinal lymphadenopathy. Pulmonary tuberculosis with hilar lymphadenopathy and associated segmental or lobar ventilation disorder*. Other forms of extra-pulmonary tuberculosis : simple pleurisy, tuberculosis of the regional lymph nodes, osteo-articular tuberculosis other than vertebral, etc.
2 RHZ / 2 RH / 4 H	In some specific cases : - pulmonary tuberculosis with nodular lesions covering a surface of over 10 cm² of the pulmonary parenchyma ; - extra-pulmonary tuberculosis with persistance of symptoms after 4 months.
2 SRHEZ/ 1 RHEZ/ 5 RHE	Smear-positive pulmonary tuberculosis already given chemotherapy for over 5 months (failure or relapse).

* *Prednisone should be added during the first four or six weeks.*

CARE FOR THE DISEASED CHILD UNTIL RECOVERY

The physician's responsibility is not confined to the choice and prescription of an appropriate chemotherapy regimen in conformity with the technical guidelines of the national tuberculosis control programme. It extends to all of the organizational measures that must be implemented by the health team, in close collaboration with the patient's family, to make sure that the treatment is administered regularly, under the best possible conditions, and is pursued until recovery.

PRETREATMENT EXAMINATION

The pretreatment examination is done by the physician. Clinical examination, sometimes completed by x-rays, shows the different localizations of the disease. Careful questioning of the child and his/her parents leads to identification of the source of infection within the family (a known, treated case of tuberculosis, or a suspected case), and provides information on what drugs the patient has been given. Questioning, clinical examination and routine biological assays (glycosuria, proteinuria) are also useful for the detection of any concurrent disease such as infectious jaundice, diabetes mellitis, epilepsy, psychomotor retardation or chronic kidney disease, which may affect the prescription or treatment management. It is essential that the child be weighed, so that dosages may be calculated on the basis of weight rather than age.

INFORMING THE FAMILY

The family should be informed by the physician during the consultation at which the diagnosis is established and treatment prescribed.

The disease itself and its treatment should be clearly explained, in comprehensible terms, to the child and the parents, with special emphasis on duration of treatment, what drugs to take (they should be shown to the patient and his/her parents, so that all will recognize their shapes and colours), how to take them (in the morning, on an empty stomach, all at once, with a few sips of water).

Talking with the parents yields information on the composition of the family (the list of individuals composing the household is used to detect contact people), living conditions, the educational level of the parents and of other children, so as to decide who will be in charge of drug administration at home. This talk aims at reassuring parents as to the child's future, and making sure that school attendance is not interrupted for more than a few weeks if he/she goes to school ; it is essential that physical culture and athletic activities be resumed gradually.

It is also useful in identifying the health unit (clinic or health centre) closest to the family's home, through which ambulatory chemotherapy will be organized with the help of the person in charge of supervising treatment of tuberculosis patients in the district.

PRESCRIPTION OF CHEMOTHERAPY

The prescription of chemotherapy by the physician must be rational, in conformity with the standardized, short chemotherapy regimens recommended by the national tuberculosis control programme, and explicited for the different diagnostic categories of tuberculosis in children.

As a general rule, ethambutol is not prescribed for children under 12 because the identification of incipient optic neuritis is difficult in

small children : however, it may be prescribed for limited periods of time, when necessary, provided close attention is paid to the dosage.

Dosage of the drugs must be strictly adjusted to the patient's pre-treatment weight. The prescription is established for the first eight weeks : both the number of drugs and the dosage are readjusted at the end of the 2nd month.

Table 13

Standardized dosage of drugs for chemotherapy regimens in childhood tuberculosis

	Initial phase two months				Consolidation phase Two/four months - Six months			
Patient's weight kg	HR Combining H 100 mg + R 150 mg	Z tab. 500 mg	S inj. mg	E tab. 400 mg	HR Combining H 100 mg + R 150 mg	HT Combining H 100 mg + T 50 mg	H tab. 100 mg	E tab. 400 mg
5 - 10*	1/2	1/2	250	—	1/2	1/2	1/2	—
11 - 20	1	1	500	—	1	1	1	—
21 - 32	2	2	500	—	2	2	2	—
33 - 50	3	3	750	2 - 3	3	H 300 mg + T 150 mg 1	H 300 mg 1	1.5-2

** For children weighing less than 5 kg, dosage must be strictly adjusted to weight, on the basis of the doses shown in the article on essential antituberculosis drugs.*

Source : Ibid. 31.

The chemotherapy regimen should be completed by the prescription of prednisone during the first four to six weeks in cases of meningitis or suffocating acute miliary tuberculosis, in tuberculosis of the serous membranes (pleurisy, peritonitis, pericarditis) and in primary tuberculosis with a segmental or lobar density caused by bronchial compression subsequent to hilar glandular enlargement. The objective of this prescription is to decrease inflammatory reactions, to prevent cerebral oedema, hydrocephalus and basilar arachnitis in case of meningitis, extensive pleural sequelae in case of pleurisy, the development of constrictive pericarditis or of intraperitoneal or pelvic fibrotic adhesions possibly generating sterility by tubal obstruction subsequent to ascitis in girls.

Evacuative pleural punctions and respiratory physical therapy are helpful in limiting sequelae and preserving the mobility of the diaphragm in case of pleurisy. Plaster casts in functional positions are often indispensable in case of tuberculosis of the limb joints.

DIRECT SUPERVISION

During the first eight weeks of treatment direct supervision of daily drug-taking by the child is an essential condition of its success. This means that the child and his/her mother must be given accu-

rate explanations, and the nurse in charge of care must give a practical demonstration, irrespective of whether the child is treated at home or hospitalized.

If the child is treated at home with a regimen that does not require an intramuscular injection of streptomycin, the mother is put in charge of treatment, and a community health agent should visit the home once a week to make sure that the drugs distributed by the clinic have been taken, provide a new weekly supply of drugs and make sure there are no adverse reactions (itching or rash, digestive disorders, jaundice).

If the regimen includes a daily injection of streptomycin at home or at the health unit, the health agent performing it is also in charge of directly supervising tablet-taking. Last, in some severe forms of tuberculosis, especially in children under four, hospitalization is required, and preferably with the mother so as to avoid a separation, improve supervision of the child and teach the mother how to administer the drugs to her little patient. A short hospital stay (one or two weeks) is also used to take the specimens needed for detection of the bacillus, to perform various initial examinations as well as evacuative punctures in serositis, supervise corticotherapy when prescribed and put a cast on a limb when necessary.

CONSULTING AGAIN AT THE END OF 2 MONTHS

Another visit is necessary at the end of the second month. In the most severe forms, this visit generally coincides with the end of the hospital stay. It is needed to check on the regression of signs of meningitis and serositis (pleurisy, peritonitis, pericarditis). In all other forms, the regression of lesions, weight gain, the disappearance of signs and symptoms are checked. In cases of initially smear-positive pulmonary tuberculosis, examination of two samples of sputum shows whether the latter have become bacteriologically negative, or at least have a considerably lower visible bacillus count upon microscopy of sputa.

At this visit, the physician checks on the regularity of drug-taking during the first eight weeks and the absence of adverse reactions, and makes sure that all of the individuals living in close contact with the diseased child have been examined.

At the end of this visit, the physician establishes a new drug prescription for the consolidation phase, in accordance with the child's weight at the end of the second month, and eliminating pyrazinamide (and streptomycin).

ORGANIZATION OF DRUG DISTRIBUTION

It is the nurse in charge of supervising treatment in the child's home district who organizes drug distribution during the consolidation phase. This is done under the responsibility of the physician and in collaboration with the personnel of the basic health unit closest to the patient's home. Once every four weeks, the necessary supply of drugs is given to the patient's parents, so that the drugs may be taken daily, at home, under the mother's responsibility.

Periodical contact, once every four weeks, between the patient's family and health workers yields information on tolerance of the drugs and on whether they are taken regularly.

If the family moves, the personnel of the basic health unit and the district treatment supervisor must inform the physician of its new address, so that all available information (initial diagnosis and treatment already received) may be transmitted to the health official in the new district, where the treatment will be pursued.

CHECKING ON RECOVERY

It is the physician who checks on recovery at the end of treatment (end of the 4th, 6th or 8th month), through clinical examination (and an x-ray, in some cases) and analysis of the patient's duly completed treatment record, corroborated by questioning of the patient and the mother. The physician must make sure that the prescribed treatment was really taken.

In case of pulmonary tuberculosis (and irrespective of the initial bacteriological status), the physician checks on recovery by performing a final chest x-ray and reviewing the findings of four microscopy examinations of sputa : two at each of the two terms, at the end of the fifth and sixth-seventh months.

Treatment failure, defined by two positive bacteriological tests on specimens taken at an interval of over 2 weeks after the 5th month and at the end of treatment, may exceptionally be seen in children receiving a short course of chemotherapy (this is more frequent in those previously given standard chemotherapy without rifampicin). A relapse is defined by two positive bacteriological tests on specimens taken at an interval of over 2 weeks in a patient having terminated a complete course of chemotherapy and considered cured. In these cases, a standardized eight-month regimen with five drugs during the first two months should be prescribed.

If there is any doubt as to the active nature of sequelae of osteoarticular tuberculosis, the neuro-encephalitic sequelae of meningitis or the neurological sequelae of vertebral tuberculosis, a specialized consultation may be needed. If signs of cortical irritation or of a motor deficit are present following meningitis, a computed tomographic scan of the brain may be valuable to determine whether tuberculosis is involved.

In some localizations, complementary surgery may be visualized after at least four months of chemotherapy : this is the case for arthrodesis in an unstable load-carrying joint following chemotherapy, pericardectomy in case of subacute constrictive pericarditis, pleurectomy or pleural decortication in case of chronic purulent pleurisy, removal of a lobe or lung in case of destruction or bronchiectasis (a delayed sequel of primary infection) and last, for the flattening of a fistula of bony or glandular origin.

This type of complement is simply corrective, and can only be recommended following a sufficiently long period of chemotherapy during which the tuberculous lesions have been sterilized.

NOTIFICATION OF CASES OF TUBERCULOSIS

The notification of cases of tuberculosis in children and their recording with a department in charge of the epidemiological surveillance of tuberculosis in the district in which the patient resides are often neglected by paediatricians or general practitioners, who view these as unimportant routine, administrative procedures.

This explains the frequent under-notification of cases of tuberculosis in children in the health statistics of developing countries.

For this reason, even when tuberculosis is diagnosed in a child by a paediatric unit, even if the second-month and end-of-treatment visits are programmed in this unit, there must be organized coordination between the paediatrics department (generally located in a city) and the department in charge of the tuberculosis control programme in the district (usually rural) in which the patient and his/her family reside, so that the treatment will be administered as well as possible until recovery (34, 35).

Neonates

Neonatal tuberculosis is an exceptional event, which may be observed in neonates in close contact with a recently detected infectious case (usually the mother). In such cases, infants showing abnormal symptoms and radiological signs compatible with the diagnosis of tuberculosis must be given a six or eight-month course of chemotherapy.

The application of short chemotherapy regimens, with strict observance of drug-taking by the ailing child for the prescribed number of months, definitively cures children of tuberculosis in 100 % of cases. The seriousness of the sequelae depends exclusively on the extent of the initial damage, and therefore on how early the disease is diagnosed.

(34) International Union Against Tuberculosis and Lung Diseases ; Tuberculosis guide for high prevalence countries. Second edition, 1991, Paris.

(35) HORNE N.W. Modern drug treatment of tuberculosis (including prevention and control). 7th edition, Ed. CHSA, London, 1990.

ESSENTIAL ANTITUBERCULOSIS DRUGS

The drugs most used to treat tuberculosis are isoniazid, rifampicin and pyrazinamide.

Isoniazid (INH)

Isoniazid is the drug of choice. It is a powerful bactericidal agent, acting both on intra- and extra-macrophage bacilli. It is easy to administer, well tolerated, has a low toxicity and is inexpensive. The presently recommended daily dose is 5 mg per kg of body weight, for children and adults. The serum concentrations induced by this dose, taken orally once a day, are 50 to 100 times the minimal inhibiting concentration, both in children who are rapid isoniazid inactivators and in slow inactivators.

Isoniazid exists in 50, 100, 150 and 300 mg tablet form. There is also a liquid form for intramuscular or intravenous injection, in ampoules dosed at 250 and 500 mg ; this dosage form is valuable in case of coma, in tuberculous meningitis. For small children, a 50 mg tablet (or half of a 100 mg tablet) should be crushed and dissolved in a fruit juice or a spoonful of fruit preserve.

Rifampicin

Rifampicin is the second major antituberculosis drug. Like isoniazid, it is active against all of the bacillary populations hosted by diseased patients. It is easy to take, well tolerated, with low toxicity at the recommended doses. It does cost more than isoniazid, however, and this limits its use. Above all, when associated with isoniazid during at least the first two months of treatment, it reduces the length of treatment. The recommended daily dose is 10 mg per kg of body weight. Peak serum drug concentration is achieved within two hours when the drug is taken on an empty stomach. This peak is over 200 times the minimum inhibiting concentration.

Rifampicin is excreted in the urine, tears and perspiration, and stains these orange or red. This peculiarity should be mentioned to the patient or his/her parents. Rifampicin comes in coated tablets or capsules, dosed at 150 and 300 mg. For children weighing less than 10 kg (and especially those weighing less than 5 kg), an oral suspension of rifampicin marketed as a syrup containing 100 mg per 5 ml or per measuring spoon is used. An oral suspension may also be prepared using the rifampicin powder contained in a capsule, and mixed with sweetened water or fruit juice.

Combination of isoniazid and rifampicin

A ready-made combination of isoniazid and rifampicin, in set proportions, does exist, and facilitates the simultaneous administration of the two drugs, thus limiting prescription dosage errors. The coated tablets or capsules come in two combination dosages :

- a "strong" one, combining 150 mg of isoniazid and 300 mg of rifampicin per tablet/capsule ;

- a "mild" one containing 100 mg of isoniazid and 150 mg of rifampicin per tablet/capsule.

To avoid confusion, the shape and colour of the two dosages are different. The combination of isoniazid and rifampicin should only be used within a national tuberculosis control programme when its bioavailability has been demonstrated : it is a fact that all of the combinations on the market are not equivalent.

Pyrazinamide

Pyrazinamide is the third major antituberculosis drug. As opposed to the previous two, its bactericidal action is only effective in an acid environment, and therefore mainly affects intra-macrophage bacilli, the persistence of which may be the cause of relapses. For this reason its action during the first two months of treatment is decisive in reducing the intra-macrophage bacillary population, and the frequency of relapses.

This drug diffuses well within the meninges. It induces minor adverse cutaneous reactions (short-lived rashes) or digestive disorders (nausea) which subside spontaneously or with symptomatic treatment and do not require interruption of treatment.

The recommended daily dose, in association with the above-mentioned drugs, is 25 to 30 mg per kg of body weight. Pyrazinamide is marketed in the form of 500 mg tablets.

Combination of isoniazid, rifampicin and pyrazinamide

There is a combination tablet, with set proportions of isoniazid, rifampicin and pyrazinamide, which facilitates simultaneous daily administration of these drugs, all three of which are indispensable during the initial phase of every chemotherapy regimen.

This set combination is marketed as a tablet containing 50 mg of isoniazid, 120 mg of rifampicin and 300 mg of pyrazinamide : the dosage to be given is 1 tablet for a weight of 10 to 14 kg, 2 tablets between 15 and 24 kg, 3 tablets between 25 and 34 kg and 4 tablets between 35 and 44 kg.

Like all set combinations, this one should only be used in a national tuberculosis control programme when the bioavailability of all three drugs, in combination, and especially of rifampicin, has been demonstrated. It is a fact that all commercial combinations are not equivalent. Other drugs are complements in the treatment of tuberculosis.

Streptomycin

Streptomycin has been used intensively in children since the discovery of its effectiveness in tuberculous meningitis. It is an aminoglycoside, which does not cross cell membranes easily : it therefore has little or no effect on intra-macrophage bacilli. Conversely, it is a very powerful bactericidal agent for actively multiplying extra-cellular bacilli, in the caseous lining of the walls of pulmonary cavitation, for instance. It also crosses the meningeal barrier easily. Its main drawback is an inability to cross the digestive barrier, and the subsequent need for intramuscular administration. Despite its effectiveness, then, its use is limited by the discomfort generated by the injection, the constraints connected with it and the difficulty, in developing countries, in sterilizing syringes and needles properly, or obtaining disposable material when there is a high risk of transmission of prevailing viral infections (be they hepatitis or HIV).

The daily dose of streptomycin is 20 mg per kg of weight in children. The usual recommended dose is 250 mg a day for children weighing 5 to 10 kg, 400 mg a day between 11 and 20 kg, 500 mg a day between 21 and 30 kg and 750 mg a day beyond 31 kg. Streptomycin (sulfate) exists in powder form, in ampoules dosed at 0.50, 1 and 5 g. The powder is diluted in water (contained in the solvent ampoule) immediately prior to use.

Thiacetazone

Thiacetazone, a member of the thiosemicarbazone family, has been extensively used in developing countries as a bacteriostatic, in association with isoniazid to prevent the selection of resistant bacilli. It does not exist separately, but is always marketed in combination with isoniazid, in set proportions, in tablets containing either 300 mg of isoniazid and 150 mg of thiacetazone (1 tablet a day in children weighing over 35 kg) or 100 mg of isoniazid and 50 mg of thiacetazone (one half to two tablets a day in children under 35 kg).

The advantages of the thiacetazone-isoniazid combination are ease of administration and low cost.

The drawbacks are poor tolerance of persons infected with the HIV, in some population groups, the high incidence of toxic adverse reactions and in some countries a limited effectiveness owing to natural resistance of the tubercle bacillus (of M.t. africanum, for instance).

Ethambutol

Like thiacetazone (and PAS in earlier times), ethambutol is a bacteriostatic at the usual doses : it therefore works in association with isoniazid or rifampicin to avoid the selection of resistant bacilli. It is usually well tolerated. Its main drawback is its toxicity when administered at high doses (25 mg/kg) for several months : the resulting retrobulbar optic neuritis is easy to detect in adults but cannot be detected at an early stage in children. The first sign of such optic neuritis is the inability to discriminate between colours, a fact which is difficult to discern in children. For this reason most paediatricians are reluctant to prescribe ethambutol in children under 12. The recommended daily dose of ethambutol is 25 mg per kg of body weight during the first eight weeks of treatment, and 15 mg per kg of body weight thereafter.

Ethambutol is marketed in tablet form, dosed at 100 mg and 400 mg.

DAILY DOSES OF ESSENTIAL ANTITUBERCULOSIS DRUGS FOR CHILDREN
(in mg/kg of weight)

Drugs	Average dose	minimum	maximum dose
Isoniazid	5	4	6
Rifampicin	10	8	12
Pyrazinamide	30	25	35
Ethambutol	25 (first 2 months)	20	30
	15 (from 3rd month on)	12	18
Thiacetazone	2,5	2	4
Streptomycin	20	15	25

COST OF ESSENTIAL ANTITUBERCULOSIS DRUGS (1)

Drugs	Dosage / form	Packaging	Price $ US*
Isoniazid	tablets 100 mg	box of 1,000	3.95
	300 mg	box of 1,000	11.07
Rifampicin	tablets 150 mg	box of 100	4.83
	(or capsules) 300 mg	box of 100	9.87
Pyrazinamide	tablets 500 mg	box of 100	4.30
Isoniazid + rifampicin	tablets 100 + 150 mg	box of 100	5.8
	150 + 300 mg	box of 100	10.2
Isoniazid + rifampicin + pyrazinamide	tablets 50 + 120 + 300 mg	box of 1,000	115**
Isoniazid + thiacetazone	tablets 100 + 50 mg	box of 1,000	5.19
	300 + 150 mg	box of 1,000	11.34
Streptomycin (sulfate)	ampoules (powder) 1 g	box of 50	13.57
Water for injection	ampoules 5 ml	box of 50	1.65
Ethambutol	tablets 400 mg	box of 500	11.90

(1) Based on the UNICEF 1991 price list.

** The FOB price (free or board) of orders through UNICEF may be calculated by adding 4 to 6 % to the price listed above.*

*** This is a special price for international organizations aiding national programmes. It includes the FOB price and the cost of air transportation.*

ISONIAZID FOR CHILDREN : 5 MG PER KG IS ENOUGH !

Whereas the effective daily therapeutic dose for adults is known to be 4 to 5 mg/kg, recommended doses for children were set as high as 8 to 10 mg/kg for many years, and sometimes as high as 20 mg/kg ! However, several studies, published in 1985 and 1986, called these practices into question, following which the Committee on Treatment of the International Union Against Tuberculosis and Lung Diseases adopted its recommendation in Singapore in late 1986, corroborated by the declaration on "tuberculosis in children", published in 1991.

PILHEU J.A. et al in Buenos Aires (Argentina) studied serum concentrations in 53 children aged 3 to 15 years who had received a single dose of 5 mg/kg of isoniazid. 35 of these children were slow inactivators of isoniazid and 18 were rapid inactivators. Serum concentrations three hours after intake of isoniazid were considerably higher than the minimum inhibitory concentration in both slow and rapid inactivators.

MICELLI J., KANTOR I. (de) et al (Argentina) studied serum isoniazid concentrations three hours after the intake of a dose of 5 mg/kg, then of another dose of 10 mg/kg two days later in 63 contact children (44 of whom were under age 7) and 16 adults. Serum isoniazid concentrations were measured using Canetti and Grosset's method. Serum concentrations were found to exceed 1 mcg/ml following absorption of 5 mg/kg of isoniazid in 90 % of children (86 % to 94 % depending on age). There was no difference between groups. The authors conclude that it is of no use to give high doses of isoniazid to either children or adults.

STEENSMA J. and NOSSENT G. in Harem (Netherlands) used Dymond and Russel's spectrophotometry method to study the serum isoniazid concentration of 45 children under age 16 who were given different doses of isoniazid. 26 children were slow inactivators and 19 were rapid inactivators. According to these findings, therapeutic isoniazid concentrations are found in the blood 2 hours and 6 hours after isoniazid intake with a dose of 4.8 mg/kg in both children and adults.

MAZOUNI M.S., AIT KHALED N., ANANE T. et al (Beni-Messous hospital), BOULAHBAL F. and KHALED S. (Pasteur Institute) in Algiers (Algeria) studied the serum isoniazid concentration three hours after intake of a therapeutic dose of 5 mg/kg, using the Canetti and Grosset method, in 49 children (including 11 under age five years) with tuberculosis. The observed concentrations were 60 to 100 times the minimum inhibitory concentration.

Subsequently to these findings, the following statement was issued by the IUATLD in 1986 : "The Committee on Treatment considers that supporting evidence provided by the information available on the subject is sufficient to recommend an equal standard isoniazid dosage both for children and adults, independently of the acetylator phenotype and the tuberculous localization. Efficient serum concentration levels of isoniazid are achieved after a dose of 5 mg/kg. Higher doses could increase both frequency and seriousness of toxic effects without any therapeutic advantage (1).

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(1) A statement of the Committee on treatment of the IUATLD. Bull. Int. Un. Tuberc. 1987 ; 62, 1-2 : 58-60.

Five years later, the Scientific Committees of the IUATLD stated : "Pharmacokinetic studies in children have shown that plasma and serum levels are frequently 50 to 100 times the minimal inhibitory concentration (MIC) for susceptible tubercle bacilli when oral doses of 5 mg/kg/day are used. Controlled clinical trials have shown that a dose of 5 mg/kg/day is well distributed by body fluids and tissues. Hepatotoxicity is rare in children ; however it does increase with increasing dose and perhaps with the concurrent use of RIF. Based on these observations and because of concern about hepatotoxicity, 5 mg/kg/day of isoniazid is recommended (2).

(2) A statement of the Scientific Committees of the IUATLD. Bull. Int. Un. Tuberc. 1991 ; 66 : 65-71.

ADVERSE EFFECTS OF ANTITUBERCULOSIS CHEMOTHERAPY

Antituberculosis drugs are generally well tolerated by children when the recommended doses are respected.

Minor adverse reactions may be observed : they include nausea or vomiting, transient itching and insomnia. They subside spontaneously or following treatment of the symptom. When seen, the effective drug doses should be checked and the patient kept under surveillance, since these signs may be harbingers of major disorders.

Systemic hypersensitivity, with a rash and systemic signs (fever, painful joints) requires that all drug intake be interrupted and the patient hospitalized. Corticosteroids are then administered until the symptoms subside and until the end of desensitization. In practice, isoniazid and rifampicin are the only drugs requiring implementation of a desensitization procedure.

To achieve this, the patient is given low doses of the essential drug, which are increased gradually until the full dose is reached. For isoniazid, for instance, the prescription is :

- on the first day : 25 mg (1/4 of a 100 mg tablet) ;

- on the second day : 50 mg (1/2 of a 100 mg tablet) ;

- on the third day : 100 mg (1 tablet) ;

- on the fourth day : 200 mg (2 tablets).

If a reaction occurs when the dose is increased, the lower dose is resumed, and the increment introduced more slowly, using two or three-day stops at each level before going on to the higher dose. When the daily therapeutic dose is reached for isoniazid, it is maintained and gradually increasing doses of rifampicin are given as follows :

- on the first day : a single 75 mg dose ;

- on the second day : 150 mg in two 75 mg doses ;

- on the third day : 300 mg in two 150 mg doses, and so on until the daily therapeutic dose for the child's weight is reached. As above, if a reaction occurs when the dose is increased, the previous dose is resumed and the increment introduced more slowly, using two or three-day stops at each level before going on to the higher dose. When the active therapeutic doses are reached for the two major drugs, the daily doses of corticosteroids are gradually reduced.

If a skin reaction develops following intake of isoniazid plus thiacetazone, this combination should be eliminated once and for all, and never again be administered to the patient.

Jaundice caused by hepatitis may be seen following the administration of isoniazid and rifampicin. Treatment should be discontinued until the jaundice subsides, and the serum transaminase concentrations have returned to normal. In most cases, the treatment may be resumed provided lower doses of the drugs are given : isoniazid 4 mg/kg of weight and rifampicin 8 mg/kg of weight. If jaundice develops again, the treatment should again be interrupted, the association of the two drugs eliminated and another association - isoniazid and ethambutol or rifampicin and ethambutol - be prescribed (without exceeding the dose of 15 mg/kg/day for ethambutol).

In case of thrombopenic purpura or of acute anuria caused by toxic tubulonephritis (both of which are exceptional), treatment with rifampicin should be permanently discontinued.

PREVENTION OF TUBERCULOSIS IN CHILDREN*

DETECTION AND CHEMOTHERAPY OF INFECTIOUS CASES OF TUBERCULOSIS

Three technical measures, of varying weight within national tuberculosis control programmes, contribute to the prevention of tuberculosis in children. The first, and by far the most important, is the ongoing detection of sources of infection and the ensuing administration of effective, standardized chemotherapy. This measure reduces the size of the germ reservoir and thus diminishes the risk of tuberculous infection in children. The second is the BCG vaccination of newborns, in countries or population groups where transmission of bacilli is intensive. This avoids early occurrence of primary infection, with its attendant major complications (meningitis, miliary and post-primary tuberculosis). The third measure only applies to individual cases in recently infected, apparently healthy infants - that is, in those with no clinical or radiological sign of disease : this is chemoprophylaxis. In developing countries where the prevalence of tuberculosis is high, this measure can only be applied routinely to healthy, non-BCG-vaccinated children, usually identified because they live in contact with a source of infection.

The best way to prevent tuberculosis in children in the framework of tuberculosis control programmes is to detect infectious patients and to cure them, using chemotherapy.

DETECTION OF SOURCES OF INFECTION

Adults constitute the vast majority of sources of infection everywhere. Of these, smear-positive cases of pulmonary tuberculosis are both the most frequent, the greatest threat to the community and relatively the easiest to detect. Actually, the detection of infectious cases raises several problems. One of the main causes of failure of national tuberculosis control programmes in developing countries is the insufficient detection of sources of infection, either because case-finding does not cover the whole country (owing to inadequate health coverage of the population at large), because it is not on-going (owing to maintenance difficulties in the microscopy laboratory network, or to difficult access to these laboratories) or for all of these reasons.

To be effective in a country where prevalence is high, the ongoing detection of sources of infection first requires the identification of suspects who consult spontaneously at the basic health unit because of their symptoms, followed by the bacteriological diagnosis of tuberculosis by microscopy of the sputa of suspects (36).

Identification of suspected cases of tuberculosis

The identification of suspected cases of tuberculosis depends on the degree of health education within the population. People over age 12 who cough and expectorate for several consecutive weeks should be encouraged to take the initiative of consulting the nearest health unit or their family doctor. Families are encouraged to

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(36) CHAULET P. La lutte antituberculeuse dans le monde : stratégies et actions sur le terrain. Respiration 1990 ; 57 : 145-159.

prefer one or the other depending on whether they have more confidence in health workers or in their doctor, both for the reception they receive and for the effectiveness of the technical response to their requests for care.

For this reason, personnel working in grassroots health units (nurses, medical aides and occasionally, general practitioners) as well as private doctors should receive special training and practice in how to deal with patients consulting with respiratory complaints. Every health worker should be able, at his/her level of competency, of identifying and treating patients with "acute" recent symptoms (caused by an acute respiratory infection of the upper airways, bronchi or lung, or by an exacerbation of a chronic bronchopulmonary condition) - the usual case - as well as those with a long history of respiratory symptoms (asthma, chronic bronchitis, bronchial dilatation). All health professionals, irrespective of where they work, must be capable of identifying the relatively small group of individuals situated between these two groups : people over age 12 years and suspected of tuberculosis, whose expectorations must be collected and examined for the establishment of a bacteriological diagnosis of tuberculosis.

The proportion of these suspects within the group of consultants depends on the health education received by the population and on the competency of the health personnel.

The efficiency of identification of suspected tuberculosis patients is enhanced by the ability of the health personnel to deal with all of the most common repiratory ailments. Nonetheless, there is also the fact that identification of suspects can be expected to cover the entire population of a country only if the health services are reasonably well distributed across its territory, and easily accessible (geographically and financially speaking).

Diagnosis of infectious cases of tuberculosis

Infectious cases of tuberculosis can only be diagnosed in a laboratory, and mainly by direct microscopic examination of the sputa of suspects. Owing to the cost of setting up and maintaining a laboratory (where direct microscopy of sputa may be performed routinely and reliably) and to the relatively low prevalence of tuberculosis, the microscopy laboratory which is mandatory for the diagnosis of tuberculosis should be located in a clinic or hospital at the seat of the health district (serving 50,000 to 300,000 inhabitants in rural areas and from 300,000 to 500,000 inhabitants in urban areas).

In developing countries, even when the prevalence of tuberculosis is high, it is usually both unnecessary (given the amount of work needed) and unfeasible (for budgetary reasons) to develop a more tight-knit network, with a national average of one laboratory per 20 to 30,000 inhabitants, for instance.

It is a fact that the personnel working in grassroots health units and private doctors are not motivated to send the sputa of tuberculosis suspects to the nearest microscopy laboratory unless the quality of the work done there is monitored and supervised at regular intervals by technicians from the province-level reference

laboratory or from a higher echelon of the health department. The quality control of district laboratories must be both permanent and periodic. There are several formulas : the central laboratory may send fixated, stained slides of sputa to be read at the peripheral level, or slides already read at the periphery may be sent to the central laboratory (all positive slides, plus one sample of negative slides), or else supervisory technicians may visit peripheral laboratories periodically.

The diagnosis of all infectious cases of tuberculosis within a country therefore requires that microscopy laboratories be decentralized so as to cover the entire population. However, the development of a network of laboratories, and the level to which they are decentralized, depend on the financial ability to cover the cost of equipping such laboratories and ensuring maintenance for them (including wages for the personnel) and on the technical feasibility of quality control.

Every person suspected of tuberculosis must furnish at least three specimens of sputum. These specimens may be collected directly at the laboratory itself, or, when the distance between the laboratory and the place of residence of suspects is too great, at the grassroots health unit. In the latter case, the necessary number of appropriate containers must be provided at that level, and health personnel at the grassroots health units be trained to obtain sputum, then to store, collect and dispatch specimens to the district laboratory.

The proportion of cases of tuberculosis diagnosed by direct microscopy of sputa with respect to suspect persons as a whole varies considerably from one country to another, on each continent : 5 to 10 % of suspects in most African and Latin American countries, 15 to 25 % in some Asian countries. It depends on the prevalence of tuberculosis, on the age structure of the population and on the quality of the microscopy laboratory network.

Role of radiological facilities

The role of radiology in the identification of suspected cases of pulmonary tuberculosis (and exceptionally, in the diagnosis of certain specific forms such as miliary tuberculosis) depends on the resources available. In most rural areas in developing countries, radiological facilities are nonexistent. The only way to identify suspected cases is therefore questioning of consultants and, when possible, their clinical examination.

However, in the chief towns of certain rural districts, as well as in urban areas, radiological facilities do exist and are available in either public or in private units. When this is the case, doctors and a varying proportion of the population resort to x-rays as a diagnostic aid in lung diseases. The danger then resides in the tendency to use chest x-rays as the main diagnostic tool for tuberculosis (to the detriment of the bacteriological examination of sputum, which is overlooked or neglected), instead of retaining its specific value as a means of identifying suspected cases of tuberculosis.

Broadly speaking, there are two possible approaches to the utilisation of available radiological facilities. When the incidence of

pulmonary tuberculosis is "moderate" - comprised between 25 and 100 cases per 100,000 inhabitants, for instance - and when an x-ray machine (or better still, and more economical, a radiophotography machine) is available, x-raying of the chest of all individuals suspected of pulmonary tuberculosis because of their chronic symptoms is useful for the identification of those who have pictures really indicative of tuberculosis as well, thus enabling the more efficient use of sputum examinations. By decreasing the number of individuals for whom such examinations are requested, the efficiency of the laboratory is increased, and repeated microscopy and requests for sputum culture may also be affected, if the laboratory facilities make this feasible. However, this policy results in a relatively high consumption of x-ray films.

When the incidence of pulmonary tuberculosis is high - 100 cases per 100,000 inhabitants or more, for instance - and when an x-ray machine is available, a chest x-ray may be indicated for all persons with chronic symptoms suggestive of tuberculosis, and whose first three sputum specimens are smear-negative. In this case, suspect x-ray pictures guide repetition of microscopy, and consumption of x-ray films is decreased.

Objectives of the case-finding strategy

Because of the difficulties encountered in detecting sources of infection, and in accordance with the inter-country differences in resources and in development of health services, the new WHO programme for the control of tuberculosis has defined differing objectives for different groups of countries, for the detection of infectious tuberculosis. The total number of infectious cases to be detected may be calculated on the basis of tuberculin surveys, which measure the annual risk of tuberculous infection in each country. The percentage of cases actually detected depends on the health coverage of the population and on the quality of the health services available.

Table 14

Objectives for the detection of cases of infectious Tuberculosis in the framework of the new who control strategy for tuberculosis

Developing countries	Annual risk of infection (%)	Rate of detection of infectious cases (%)
low income, poorly developed health system (Africa, Indian subcontinent)	1.0 - 2.5	60 - 65
medium-level income with relatively developed health system	0.5 - 2.5	85
Eastern and south-eastern Asia	1.0 - 2.5	80
Latin America, Middle East, North Africa	0.5 - 1.5	90

Source : KOCHI A. The global tuberculosis situation and the new control strategy of the World Health Organization. Tubercle 1991 ; 72 : 1-6.

When the health system is not very developed, the organization of a network of microscopy laboratories covering the entire territory should make it possible to detect at least 2/3 of infectious cases (60 to 65 %) at all times. When the health system is relatively developed and makes more extensive use of radiology and laboratory facilities, 80 to 90 % of the sources of infection present in the community may be detected.

The detection of sources of infection enhances protection of children. Children living in contact with infectious cases are exposed to a high risk of infection ; health workers should therefore examine them carefully to make sure they have a vaccinal scar and perform BCG vaccination if they have not been vaccinated, and to detect any (infrequent) cases of extra-pulmonary or pulmonary tuberculosis.

CHEMOTHERAPY OF INFECTIOUS CASES

Standardized chemotherapy of all identified infectious cases is the basic element of all national tuberculosis control programmes. At present, this chemotherapy for both children and adults is essentially based on short, 6 to 8-month courses, standardized in accordance with each national context.

Identification of infectious cases

Three broad categories of infectious cases must be identified (37), and for each of these categories, of differing size, appropriate chemotherapy regimens have been recommended by WHO.

New cases of infectious pulmonary tuberculosis

This category includes cases of smear-positive pulmonary tuberculosis (or with positive culture and extensive x-ray lesions), previously untreated or treated for less than one month. The risk of bacterial resistance to isoniazid and/or rifampicin is low in such cases. This category represents the vast majority of infectious cases identified each year (80 to 95 %). The recommended chemotherapy regimen involves two phases :

- an initial intensive two-month (eight weeks) phase with an association of isoniazid, rifampicin, pyrazinamide and a fourth drug : streptomycin or ethambutol, preferably administered daily ;

- a four-month consolidation phase, during which isoniazid and rifampicin are given daily, or three days a week (every other day) when totally supervised administration of drugs is feasible.

This combination of isoniazid and rifampicin is relatively expensive. For this reason it may be replaced by another daily combination, of isoniazid and thiacetazone (or ethambutol), which should be given for six months : the total treatment then lasts eight months. In countries where prevalence of HIV infection is high, ethambutol should be preferred to thiacetazone owing to the high frequency of adverse reactions.

Cases having previously undergone chemotherapy

This second category, which represents 5 to 20 % of the infectious cases identified each year depending on the country, contains cases of infectious pulmonary tuberculosis which have already received a complete or incomplete course of chemotherapy : in other words, smear-positive cases. There are those who come back after having prematurely, spontaneously interrupted

(37) *Ibid. 31*

their treatment (false failures) or those who have completed their course but have two positive bacteriological examinations during the last two months of treatment (true failures), and last, those who were considered cured after a complete course of treatment, but had two positive bacteriological examinations during the months following completion of the treatment (usually during the first two years following the end of treatment (relapses).

The risk of acquired bacterial resistance to isoniazid and/or streptomycin, and occasionally to rifampicin, is higher among these cases than among new cases. The recommended chemotherapy regimen for this category of cases always extends over eight months and involves two phases :

- an initial intensive three-month phase combining isoniazid, rifampicin, pyrazinamide and ethambutol daily (with a daily supplement of streptomycin during the first two months) ;

- a five-month consolidation phase combining isoniazid, rifampicin and ethambutol, given daily or three days a week when totally supervised administration of drugs is feasible.

This regimen effectively cures patients whose bacilli remain sensitive to antibiotics or are resistant to isoniazid only, or to isoniazid and streptomycin.

Table 15

Categories of cases of infectious pulmonary tuberculosis and corresponding chemotherapy regimens*

Categories	Chemotherapy regimen of choice	alternative
New cases of smear-positive pulmonary tuberculosis (or with positive culture only) never treated or treated for less than one month	6 months 2 SRHZ/4RH (or 4 R3 H3) 2 ERHZ/4 RH (or 4 R3 H3)	8 months 2 SRHZ/6 TH 2 SRHZ/6 EH
Cases of bacteriologically positive pulmonary tuberculosis having received one course of chemotherapy	8 months 2 SRHEZ/ 1 RHEZ/ 5 RHE or 5 R3 H3 E3	
Chronic cases of bacteriologically positive pulmonary tuberculosis having already received 2 courses of chemotherapy or more	12 months 3 Th CK/9 Th C	permanently H only

** The initials stand for drugs : S = streptomycin ; R = rifampicin ; H = isoniazid ; Z = pyrazinamide ; T = thiacetazone ; E = ethambutol ; Th = ethionamide ; C = cycloserine ; K = kanamycin.*

The figure in front of each group of letters shows the number of months during which the drugs are administered. A figure following a letter shows the number of weekly doses of that drug.

Chronic cases of infectious pulmonary tuberculosis

This third category continues to excrete bacilli following completion of more than two courses of chemotherapy including isoniazid and rifampicin. Such cases are relatively uncommon, and

when frequent they are indicative of the poor quality of application of chemotherapy within the community (erroneous or anarchic prescriptions, lack of supervision and control). The vast majority of these cases host bacilli that are resistant to isoniazid and to rifampicin (at the least) and their recovery is improbable.

In those countries where it is economically feasible, a twelve-month course of chemotherapy associating second-line antituberculosis drugs which have never been given before (such as ethionamide, cycloserine, kanamycin or capreomycin) may be used when sensitivity tests have confirmed bacterial resistance to all previously used drugs ; this regimen is relatively toxic and is less effective than the above-mentioned regimens.

In countries where resources are limited, and when second-line drugs are not available, the only alternative is to treat these chronic excreters of resistant bacilli with a single drug, isoniazid, in the hopes of making them less infectious.

In developing countries the highest priority must be given to the organization of treatment for the first two categories of patients, so as to prevent the multiplication of cases belonging to the third category.

Special care

In the framework of national tuberculosis control programmes (38), infectious cases must be given special care until they are cured. The organization of this management is the responsibility of public health services, since it is a part of the overall prevention policy. Private doctors should be associated in the implementation of national tuberculosis control programmes : they may contribute to the care of patients by advising them, referring them when they observe any irregularity in the course of treatment, or new symptoms linked with adverse reactions or a concurrent disease.

Recording of cases, distribution of drugs

Recording of cases of tuberculosis within each district is the basis for monthly and quarterly notification of cases to the central authorities. Antituberculosis drugs should be distributed to recorded patients free of charge or for a modest lump sum, by the health structure closest to their home. This drug distribution should be monitored constantly during the initial phase of treatment (2 or 3 months), then periodically (once a week or once a month) during the consolidation phase. Constant monitoring of the initial, intensive phase of chemotherapy for infectious cases is the key to successful treatment. It must be carefully organized and does not necessarily imply hospitalization of patients.

Days of distribution and amounts of drugs supplied should be mentioned in the patients' individual file or on their treatment record card.

Bacteriological monitoring of expectoration (by microscopy of sputum smears) must be performed at the end of the second or third month of treatment, and above all at the end of each of the last two months of treatment.

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(38) Ibid. 34.

Procedures for contacting patients who are seen irregularly or are absent are put into action when treatment is interrupted for more than one week : recording of several addresses at the outset (home, parent's address, place of work or school, neighbours and/or friends) facilitates such contact.

Evaluation of treatment

The analysis of the outcome of trimestrial or annual cohorts of infectious cases (with new cases and old cases or "relapses" analysed separately) is useful in measuring the impact of chemotherapy applied in the framework of national tuberculosis control programmes. This is the basic method for evaluating treatment results (39).

At the end of treatment, or one year after the beginning of treatment, the annual cohort of cases of infectious pulmonary tuberculosis is divided into six categories depending on their outcome at the chosen time.

1. Cured cases, having received a complete course of treatment and with at least two negative bacteriological results at the end of treatment.

2. Cases which received a complete course of treatment but had no bacteriological assay at the end of treatment or had only one negative result.

3. Failures (or relapses) with two positive results or a single positive result and radiological deterioration, and which must be given another course of chemotherapy.

4. Patients deceased (the cause being tuberculosis, other or unknown).

5. Patients lost sight of before the end of treatment, who interrupted their treatment before the end and did not come to get their drugs for more than two consecutive months.

6. Patients who moved in the course of treatment, and are in the hands of health personnel from another health unit.

Objectives of the treatment strategy for infectious cases

The new WHO programme for the control of tuberculosis has modified the objectives for the rate of cure to be achieved by national programmes, owing to the specific difficulties encountered in implementing treatment strategies in many countries (irregular, insufficient supply of drugs, second-line drugs not available, inadequate numbers and competence of health personnel for ensuring supervision of treated patients until their recovery).

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(39) Ibid. 34.

Table 16

Objectives to be achieved for rate of cure of infectious cases in the new who control strategy for tuberculosis

Country	Length of chemotherapy course for all new cases	Rate of cure (%)
low income, with poorly developed health systems	8 months	85
medium-level income with relatively developed health system	6 months	85
industrialized, with low incidence of tuberculosis	6 months	95

Source : KOCHI A. The global tuberculosis situation and the new control strategy of the World Health Organization. Tubercle ; 1991, 72 : 1-6 and Ibid. 31.

The percentage of patients deceased, lost sight of, transferred and in failure should not exceed 15 %. The rate of cure actually is somewhere between 85 and 95 %. These rates have been achieved in many developing countries under actual conditions of programme implementation : in Asia (Korea, Vietnam, China), in Africa (Tanzania, Mozambique, Benin, Algeria) and in Latin America (Nicaragua) in the framework of the application of independently managed national programmes or those benefitting from the assistance of the IUATLD (International Union Against Tuberculosis and Lung Diseases), WHO and the World Bank.

Given the feasibility of achieving a high rate of cure of identified cases of infectious tuberculosis everywhere, it is obvious that the reduction of the germ reservoir in each country is directly linked with the results of the strategy for case-finding. It is this reduction of the germ reservoir within the community, the cumulative result of a well-directed case-finding strategy and an adequate treatment strategy, which constitutes the main technical measure for the prevention of tuberculosis in children.

Conclusion

A 50 % drop in the global incidence of tuberculosis is feasible in the coming decade provided infectious cases are detected and given chemotherapy, in accordance with the technical guidelines issued by the IUATLD. Children will be the first beneficiaries of this strategy, after the patients themselves. As was the case in the industrialized countries during the first half of the 20th century, a reduction in the incidence of infectious tuberculosis will immediately result in a drop in the annual risk of tuberculous infection, and in the number of latent or patent primary infectious in young children, of extra-pulmonary localizations of tuberculosis in children

and of pulmonary cases in adolescents. For this reason, case-finding and chemotherapy for cases of infectious tuberculosis, which mainly occur in adults, represent the choice technical measures for the prevention of tuberculosis in children.

Table 17

Dosage of antituberculosis drugs in adults with infectious tuberculosis

Drugs (mg)	Administration						
	daily					intermittent 3 times/week	
	HR 150 + 150 150 + 300	Z 500	E 400	S 1 g	HT 300 + 150	HR 100 + 150 150 + 300	E 400
Pretreatment weight 33 - 50 kg	3 (150 + 300)	3	2	750 mg	1	3 (100 + 150) + H 300	3
51 kg or more	2	4	3	1 g*	1	4 (150 + 300) + H 300	4

** 750 mg after age 50.*
R = rifampicin ; H = isoniazid ; Z = pyrazinamide ; S = streptomycin; HR = isoniazid + rifampicin ; HT = isoniazid + thiacetazone.
Source : Ibid. 31.

CHEMOPROPHYLAXIS OF TUBERCULOSIS IN CHILDREN*

Chemoprophylaxis, or preventive chemotherapy, of tuberculosis in children aims at avoiding the transition from infection to disease in children recently infected with the tubercle bacillus. In earlier times, in Europe, these children were identified with the help of tuberculin tests which were performed yearly within school health check-up programmes. The consequence of this practice - a twelve-month course of chemoprophylaxis for newly infected children - is still enforced in some developing countries where school attenders represent only a fraction of the school-age population, despite the lack of clear evidence of its value for reducing the incidence of the disease in the current context of national tuberculosis control programmes.

The fact is that in developing countries today, BCG vaccination has been broadly administered in the framework of the expanded programme on immunization. In most countries, 80 to 90 % of children have received the BCG by age one, and almost 100 % are vaccinated by the time they reach school age. Since the tuberculin test is incapable of distinguishing recent infection from immunization, the number of children who may be considered to be recently infected is limited : they may only be found among non-BCG-vaccinated children living in close contact with a source of infection.

This explains why national tuberculosis control programmes in developing countries prescribe chemoprophylaxis of tuberculosis in children only as a measure applying to groups of at-risk chil-

*** By Mourad BAGHRICHE, Nadia AIT KHALED, Pierre CHAULET.**

dren : that is, apparently healthy children (showing no clinical or radiological sign of disease) who have not been given the BCG and who run an accrued risk of incurring natural infection because they live in contact with a source of infection.

WHICH PREVENTIVE CHEMOTHERAPY?

The only preventive chemotherapy recommended for children at the present time is the daily administration of isoniazid only, at the dose of 5 mg/kg, for a period of 6 months (40, 41).

Alternative preventive chemotherapy schemes presently under study for infected adults with a high risk of endogenous reactivation (HIV seropositive subjects, drug abusers,...) are based on the administration of rifampicin only or of a combination of isoniazid and rifampicin (or of rifampicin and pyrazinamide) for two or three months. However, these regimens are not appropriate for national tuberculosis control programmes in developing countries, firstly because there is still no evidence of their superiority over chemoprophylaxis using isoniazid only, and secondly because the available resources are not even sufficient for the implementation of curative chemotherapy for all infectious patients, with two months of isoniazid, rifampicin and pyrazinamide in association during the first two months.

Only a few years ago the recommended duration of preventive chemotherapy was twelve months. This duration is now limited to six months, owing to the effectiveness of modern curative chemotherapy, which rapidly reduces the infectiousness of cases of tuberculosis considerably, and cures them within six to eight months.

There is a very small bacillary population present in the organism of a recently infected child with no clinical or radiological symptoms of primary infection. This population is considerably reduced or even totally destroyed by isoniazid within weeks. It would be paradoxical to extend chemoprophylaxis beyond six months (for a dubious gain) in healthy children living in contact with a source of infection which in turn is cured by a six-month course of curative chemotherapy.

PREVENTIVE CHEMOTHERAPY : FOR WHICH CHILDREN?

Preventive chemotherapy is never indicated for healthy, BCG-vaccinated children with a vaccinal scar, irrespective of their age and of intensity of contact : the tuberculin test itself does not reliably differentiate post-vaccinal allergy from natural infection.

The question of preventive chemotherapy only arises for healthy, non-BCG-vaccinated children or those with no vaccinal scar, living in contact with a source of infection, and in accordance with the results of the tuberculin test.

In healthy, non-BCG-vaccinated tuberculin-positive children (that is, with an induration of 5 mm or more, 72 hours after the intrader-

(40) Tuberculosis in children. Guidelines for diagnosis, prevention and treatment (a statement of the scientific committees of the IUATLD). Bull. Un. Int. Tub. Lung. Dis. 1991 ; 66 : 61-62.

(41) SJOGREN I. Diagnostic categories in childhood tuberculosis. Bull. Un. Int. Tub. Lung. Dis. 1985 ; 60, 1-2 : 77-79.

mal injection of purified tuberculin), the decision depends on the child's age :

- if the child is under 5 years old, recent infection is highly probable and preventive chemotherapy is always indicated ;

- if the child is aged 5 to 14, and medical records prove that tuberculin tests performed during the last two years were negative, a positive tuberculin test is proof of recent infection : preventive chemotherapy is indicated. More often, there are no such documents and no way of knowing whether the infection is recent or old. In this case, preventive chemotherapy is not indicated, but the child should be kept under special surveillance for two to three years. His/her parents should be informed of the risk of disease, and of the need to consult if any abnormal symptom develops.

In healthy, non-BCG-vaccinated, tuberculin-negative individuals, BCG vaccination should be performed as soon as possible, as a rule, whereas the source of infection must be actively treated.

There is one exception, however : children under 12 months old, for whom preventive chemotherapy may be indicated. It is a fact that a neonate or infant under 12 months old who has not been given the BCG and is in close contact with a known source of infection (usually the mother) may have been infected recently and be in the ante-allergic phase at the time of the tuberculin test. For this reason such children, who have not yet received the BCG, should be given isoniazid only every day for three months, after which another tuberculin test will be performed. If the second test is positive, preventive chemotherapy with isoniazid should be continued until the end of the sixth month. If the second tuberculin test is still negative, the child should be given the BCG.

A SPECIAL CASE : HIV-SEROPOSITIVE CHILDREN

Owing to the extension of the HIV/AIDS epidemic in countries with a high prevalence of tuberculosis, and more particularly in subsaharan Africa and Asia, there is a non-negligeable risk for children in these countries (and especially in cities and in the poorest contexts) of infection by both the HIV and the tubercle bacillus. For this reason, tuberculin-negative asymptomatic (apparently healthy) but seropositive children (or born to seropositive mothers) should receive the BCG vaccine, whereas asymptomatic, tuberculin-positive children should be given preventive chemotherapy with isoniazid. The optimal duration of this chemotherapy (six or twelve months) has not yet been determined (42).

In developing countries where BCG vaccination of neonates is extensively practiced, preventive chemotherapy or chemoprophylaxis is a preventive measure to be applied to healthy, non-BCG-vaccinated children living in contact with a source of infection. The three groups of children requiring treatment are :

- healthy children under 5, non-BCG-vaccinated but tuberculin-positive ;

- healthy children aged 5 to 14 whose tuberculin reaction has been positive for less than 2 years ;

(42) Ibid. 34.

- children under one, non-BCG-vaccinated, initially tuberculin-negative and recently become tuberculin-positive.

BCG VACCINATION*

The prevention of tuberculosis consists of avoiding infection in receptive individuals. Only by eliminating the sources of infection - that is, infectious cases - can this goal be achieved. For this reason, case-finding and treatment are of the utmost importance.

Given the impossibility of eliminating all infectious cases, it is important to protect receptive individuals by immunization. This may be administered to children in early infancy, before they have had time to become infected and to catch a severe form of disease. However, the protection afforded is not total and does not last forever.

TECHNICAL REVIEW

Age group

Most countries respect the WHO recommendations, according to which neonates should be vaccinated as early in life as possible. The BCG is performed on all previously unvaccinated children when brought to a health centre.

In all cases, vaccination is performed without prior tuberculin testing, and is said to be indiscriminate.

The vaccine

The BCG is a live, bacterial vaccine prepared from the bovine tubercle bacillus, attenuated by 230 passages on bile-glycerine-potato medium. It is available as a lyophilized (vacuum-dried) powder. The ampoule containing the dry vaccine is heat-sensitive and must therefore be refrigerated, or even put in deep-freeze. It is also sensitive to light and is often placed in coloured glass ampules. When this is not the case, ampules are delivered with dark paper or aluminum foil wrapping, which should be placed around the ampoule during use. Another ampoule, containing a solvent which varies from one manufacturer to another, comes with the ampoule of dry vaccine. This solvent must be cold when used - that is, it requires at least 24 hours of refrigeration.

Once the solvent has been added to the powder, the vaccine must be kept refrigerated and used within the next 3 to 4 hours. The main vaccines quality-approved by WHO and available worldwide through distribution by UNICEF are the Pasteur Paris and the Tokyo vaccines.

VACCINAL TECHNIQUE

Preparation of the vaccine

The vaccine is prepared using a sterile 5 ml syringe and a long, large needle (diameter 0.8 mm, length 30 or 40 mm, conventionally designated as 0.8 x 40 mm, or, according to the system prevailing in English-speaking countries, 22G 1 1/2). All of the solvent is drawn into the syringe, and then gently evacuated along the side of the ampoule, into the powdered vaccine. The ensuing liquid is then pumped in and out of the syringe repeatedly so that the powder is completely dissolved.

Use of the vaccine

A special syringe is used : it may be a plastic or glass 1 ml syringe equipped with a needle for intradermal injections - that is, short and fine (diameter 0.45 mm, length 10 mm, conventionally designated as 0.45 x 10 mm or, in the system of English-speaking countries, 26G 3/8). Syringes and needles are either disposable, in

*** By Nicole GUERIN and Patrick BREGERE.**

For the cold chain, see Children in the Tropics, n° 162/163 (1986).

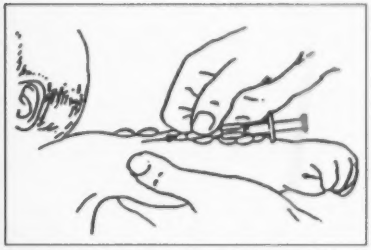
which case they are destroyed after use, or reusable and sterilized by prolonged boiling in water with no added antiseptic.

The skin of the mid-part of the anterior side of the left forearm or of the posterior side of the upper left arm is disinfected, using absorbent cotton dipped in alcohol. It is important that vaccination be systematically performed in the same place throughout a country, so that vaccinated children may be easily identified by their scar, always at the same place.

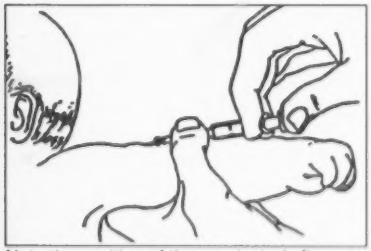
The amount of BCG suspension required to vaccinate one child is drawn into the intradermal injection syringe. The amount injected depends on the child's age : 0.05 ml for infants under age one, and 0.1 ml thereafter. The injection must be strictly intradermal, in the superficial layer of the skin. If the needle penetrates too deeply, the vaccine should not be injected : the needle should be withdrawn and introduced again at an adjacent site. A properly performed intradermal injection causes a raised wheal 7 to 9 mm in diameter to form instantly, and the skin on it takes on an "orange peel" consistency. The drop of vaccine remaining on the skin is then dried, and the arm left uncovered.

Vaccinal aftermaths

The evolution of the local lesion is always the same. The wheal produced by vaccination disappears within a half-hour. Three to four weeks later, a small, red, indurated nodule develops, and grows to 6 to 8 mm in diameter. It may remain unchanged for one to two months. Often, the skin thins, an opening occurs, and some fluid is released. Within some weeks, two to eight as a rule, the flow stops and a scab develops, persists for some time then falls off, uncovering a rounded, slightly depressed and discoloured scar measuring about one-half centimeter across. At no point should any substance be applied to the lesion.



Note the angle between needle and skin.



Note the position of the vaccinator's fingers.
Technique of intradermal vaccination.
Source : Vaccination en pratique. OMS, 1984

Parents and teachers should be informed of this process, and nurses and doctors should be familiar with and explain it. No substance should be used to clean the vaccinal lesion at any point in the process.

In one case out of about one thousand, however, and particularly in children under age one, a swollen gland may develop in the armpit or in the elbow crease. The evolution of this gland should be watched carefully, and it should be punctured if it grows larger and the skin becomes thin and somewhat purple. In some cases it may fistulate. Recovery occurs spontaneously after some time in all cases ; the only thing to do is to cover the wound with a dry dressing.

In the last decade or so, actual epidemics of post-BCG fistulized lymphadenitis have been recorded from time to time. Careful analysis of these outbreaks has shown :

- that some workers were not aware that neonates must be given 0.05 ml rather than 0.1 ml ;
- that the vaccine is often improperly prepared : either too much or too little solvent is dissolved in the pow-

dered vaccine, or else there is insufficient homogenization of the suspension, and the vaccine administered is too concentrated to some cases and insufficiently concentrated in others ;

- that the injection is sometimes done too deeply ;

- last, that some vaccines are "stronger" than others. This is the case of the Pasteur BCG, in particular, and is often the cause of outbreaks of lymphadenitis. A recent change in the vaccine supplier and insufficiently strict vaccination techniques explain these incidents, then. UNICEF is now careful not to supply a country with a vaccine to which it is not accustomed. Further, the manufacturer has modified the concentration so that it will be more appropriate for the vaccination of neonates.

Other more serious complications - osteitis or disseminated infection - are extremely infrequent, with less than 1 case per one million vaccinations performed and in the latter case are often linked with immunodeficiency.

Contraindications

Contraindications to vaccination are extremely uncommon.

Theoretically, children with congenital or acquired immunodeficiency should not be vaccinated. Similarly, children with clinical signs of AIDS are excluded from vaccination.

However, a confirmed diagnosis of this type is exceptional in neonates, and it is probable that some children in these categories are vaccinated. A review of findings for children born to HIV-positive mothers and given the BCG before the diagnosis was made shows that hardly any problems occurred.

Post-BCG lymphadenitis developed and regressed, often with the help of treatment ; systemic BCG infection has been described in one adult vaccinated for therapeutic purposes in the presence of clinical signs of Kaposi's syndrome. The risk of developing tuberculosis far outweighs any complications ensuing from BCG vaccination.

Possible vaccinal associations

Other vaccinations needed by the child may be administered on the same day, but on different parts of the body. Since 1984, WHO recommends that neonates be given a dose of oral poliomyelitis vaccine on the same day as the BCG vaccination. If the BCG is performed at age two months or later, combined diphtheria-tetanus-pertussis immunization may also be performed concomitantly. From nine months on, the measles vaccine may be injected on another site on the same day as the BCG. All of these associated vaccinations have proved to be harmless for each other, to be no less active and induce no more adverse reactions than when administered alone.

Controls

Actual immunization is confirmed by the presence of a scar. When necessary, a tuberculin survey may be performed to make sure that the vaccination was technically well done. When such surveys are conducted, they should cover only a sample of children. Correct intradermal vaccination induces positivation of tuberculin tests in about 90 % of children within one year (three to twelve months) of vaccination. It is customary for school health departments to check on the immune status of a sample of six year-olds from time to time. As a rule, the percentage of children vaccinated at birth and who retain a positive tuberculin reaction at age six

does not exceed 30 to 50 %. This justifies routine revaccination of children during their first year at school, when feasible, in those countries where the risk of infection remains high, but such a strategy is of course costly.

Table 18

Results of some studies on the protective efficacy of BCG vaccine

Place of study and date	Study population	Vaccine used	Comments
Boksburg-Benoni Hospital, South Africa 1972-1976	Blacks 0 - 4 year-olds	Tokyo (after October 1972)	19 cases vaccinated, 0/8 with meningitis. Efficacy > 60 % for all forms, 100 % TB meningitis
Rangoon Children's Hospital, Myanmar (Burma) July 1982	0 - 4 year-olds	Tokyo (half-dose)	Efficacy 38 % for all forms, 52 % TB meningitis, 80 % disseminated TB
Israël 1956-1979	Jewish 0 - 12 year-olds	Glaxo (after late 1960s)	Age - and sex-adjusted efficacy, 24 % for pulmonary TB, 64 % for extra-pulmonary TB
Bangkok Central Chest Clinic Sept. 1981 - June 1984	0 - 4 year-olds	Mérieux	Efficacy 53 % for all TB, 72 % for bacteriologically confirmed cases
Manitoba, Canada 1979-1983	Amerindians 0 - 14 year-olds	Connaught	Efficacy > 60 % for all TB, 73 % for bacteriologically confirmed cases
Lomé, Togo 1983-1985	0 - 6 year-olds	Glaxo	Efficacy 61.5 %, higher for more severe disease and chidren under 6 years of age
Seoul, Korea, 1984-1986	< 5 years	Paris seed lot n°1173P2 produced by Japan BCG Laboratory	Efficacy 74 % Unpublished study

Source : MILSTIEN J.B., GIBSON J.J. Bulletin of WHO ; 1990

Protection afforded by the vaccine

Controversies over the efficacy of the BCG broke out as soon as the vaccine was made available. Numerous controlled trials have been conducted since 1930, with results ranging from 0 to 80 %. The findings of the most recent studies are summarized in table 18. Variations may be explained by the characteristics of the different vaccinal strains and by the differences between the clinical forms of tuberculosis studied (the vaccine affords better protection against severe meningeal and miliary forms than against other forms of tuberculosis). The intensity of infection may also play a role, as well as the frequency of infections with atypical mycobacteria. In fact, the immunological mechanisms involved in tuberculosis and in antituberculosis immunization are still poorly understood.

Vaccinal policies

With thirty or even forty years of massive use and close to one hundred million vaccinations a year, the BCG remains the most widely used vaccine in the world. The global proportion of children under age one having received it was 89 %, according to WHO estimations in April 1991. It is a fact, however, that the elimination of tuberculosis cannot be achieved by the universal immunization of children, but rather by the detection and treatment of infectious cases.

When neonates run only a negligeable risk of developing the disease, immunization of all children becomes unnecessary. Specialists estimate the threshold for annual risk of infection, below which immunization is no longer valid, at 0.01 per 100, or 1 per 10,000. Several European countries such as Sweden and Czechoslovakia have experimented the discontinuation of systematic immunization and maintained it for exposed population groups only, for a period of time. The resulting rise in the number of cases of tuberculous meningitis in children was only temporary, and BCG vaccination has been permanently discontinued. Other countries are considering a similar solution for the coming years.

Nonetheless, the increasing number of cases of tuberculosis observed in the USA since 1986, and which seem to be directly linked with the global AIDS epidemic, cause bewilderment as to the best policy in decision-makers, particularly since the recrudescence particularly affects infectious cases.

MANAGEMENT OF A CHILD WITH A POSITIVE TUBERCULIN TEST*

A positive tuberculin test reaction - that is, an induration with a transverse diameter of 5 mm or more 72 hours after the intradermal injection of tuberculin - may be caused either by BCG vaccination or by natural infection or reinfection.

A number of studies have suggested that an induration diameter exceeding 12, 14 or 15 mm is indicative of recent infection, even in a BCG-vaccinated child. Actually, the published data are insufficient for the definition of a definite cut-off point beyond which recent superinfection would be confirmed for individual cases. This is why the size of the induration does not definitely discriminate between post-BCG vaccinal allergy and natural infection, for clinical purposes, nor does it prove the more or less recent nature of the infection in any given child.

What to do?

- first, question the parents : was the child given the BCG, and when?

- then examine the child carefully to determine the existence of a vaccinal scar on the upper arm or forearm (depending on the country) and look systematically for abnormal clinical signs ;

- if any clinically detectable abnormality is present, seek proof of lymph node, peritoneal, meningeal, osteo-articular or any other form of tuberculosis. If the child has respiratory symptoms and above all, if he/she lives in contact with a known source of infection, a chest x-ray is mandatory for the detection of possible pulmonary tuberculosis.

If the child is apparently healthy, with no clinical or radiological sign suggestive of tuberculosis disease, the positive tuberculin reaction is not of pathological portent when the BCG has been performed and is certified by the presence of a vaccinal scar. In such cases, there is no reason, and no justification for the prescription of preventive chemotherapy. There is only one exception : a vaccinated child in contact with a source of infection and whose intradermoreaction exceeds 15 mm. The hypothesis of recent infection is plausible then, and although the utility of chemoprophylaxis has not been proved, many paediatricians do prescribe it in such cases.

Conversely, if the BCG has not been administered or if no vaccinal scar can be found, the positive reaction to tuberculin should constitute a presumption of latent primary infection. Two cases are distinguished :

1. Primary infection is definitely recent if the child is under age 3. In practice, the infection should be considered as probably recent in all children under 5, and preventive chemotherapy undertaken.

2. In children aged 5 to 14, when no document is available proving the existence of a negative tuberculin reaction in the last two years, preventive chemotherapy is not necessary. If on the other hand such documents are available, preventive chemotherapy should be prescribed.

In all cases, the source of infection should be actively sought among the people living in close contact with the child, and especially in the parents and other adults living in the same household.

*** By Pierre CHAULET and Nadia AIT KHALED.**

AN ALGERIAN EXPERIMENT : SHORT CHEMOTHERAPY FOR TUBERCULOSIS*

Since 1980, in the framework of the Algerian national tuberculosis control programme, the basic course for the treatment of tuberculosis in both children and adults is a daily chemotherapy regimen over a six-month period. The experience of a paediatrics department in Algiers shows the outcome in 427 children suffering from tuberculosis diagnosed by the same medical team between 1979 and 1985, all given a short course of chemotherapy lasting six months, with a follow-up of two years or more after the end of chemotherapy.

MATERIAL AND METHODS

SUBJECTS

The group studied was composed of the 427 children hospitalized in the Paediatric Clinic of the Beni-Messous University Hospital Centre (Algiers) between 1st July 1979 and 31 January 1985. Once tuberculosis was diagnosed, all were given a short, six-month course of chemotherapy. These cases were registered consecutively and no selection was made.

The general characteristics of this group show : an equivalent gender distribution, few children under age 4 (explained by the intensive application of BCG vaccination at birth in the area served by the hospital) and a relatively satisfactory nutritional status in these urban and suburban-dwelling children.

Table 19

Subjects : general characteristics

Characteristics	No.	%
male	206	48
female	221	52
Age 0 - 4 years	100	23
5 - 9 years	148	35
10 - 15 years	179	42
Nutritional status		
normal	290	68
Gomez degree I*	42	10
Gomez degree II	66	15
Gomez degree III	29	7

** Gomez classification (WHO) measuring weight deficit : degree I : 10 to 25 %, degree II : 25 to 40 %, degree III : over 40 %.*

Bacteriological or histological confirmation of tuberculosis was only obtained in 44 % of cases. In the remaining 56 %, diagnosis was established on the sole basis of clinical and above all radiological evidence, on the results of the tuberculin test and the patient's history (contact with a source of infection).

* By T. ANANE, J. CERNAY, A. BENSENOUCI, A. ZAOUCHE, H. BOUKHELAL, S.E. LAALAOUI, J.P. GRANGAUD, M.S. MAZOUNI.

Table 20

Diagnosis of tuberculosis in children in Algiers

Diagnosis	No.	%
Bacteriology		
smear-negative, positive culture	78	18
smear-positive and culture positive	32	8
smear-positive only	23	5
Cyto-histology (caseation or tuberculous follicle)	53	13
Total	186	44
Presumptive bacteriology/histology negative or not performed	241	56

The frequency with which bacteriological or cyto-histological proof of tuberculosis is obtained depends on the localization of the disease : it is greater in pulmonary localizations (bacteriological confirmation) and regional lymph nodes (cyto-histological confirmation) than in the other localizations.

Table 21

Diagnostic confirmation (bacteriological or histological) of tuberculosis in children according to localization of the disease

Localization	Number of cases	Confirmed cases No.	Confirmed cases %
Pulmonary (total), of which	157	103	66
pulmonary, non cavitary	65	29	44
pulmonary, cavitary	68	56	82
pulmonary, miliary (alone or associated)	24	18	75
Mediastinal	134	11	8
Pleural	56	10	16
Meningitis only	7	4	57
Regional lymph nodes	46	42	91
Osteo-articular*	12	5	42
Other localizations**	15	11	73

** Pott's disease : 7, other : 5.*

*** Peritonitis : 11, intestinal : 2, pericarditis : 1, renal : 1*

CHEMOTHERAPY REGIMENS

All 427 children received one of the two daily short (six months) courses of chemotherapy defined in the national tuberculosis control programme :

- either the 2 SRHZ/4RH regimen associating isoniazid (H) and rifampicin (R) every day for six months, with a daily supplement of

streptomycin (S) and pyrazinamide (Z) during the first two months (in cases of pulmonary, meningeal, osteo-articular or renal tuberculosis) :

- or the 2 RHZ/4RH regimen, the same as the former but without streptomycin during the initial phase (for all other forms of tuberculosis : patent primary infection, regional lymphadenitis, pleural, peritoneal and other localizations).

Prescription of doses was standardized.

Table 22

Prescribed doses of antituberculosis drugs

Drugs	Daily dose in mg/kg	
	Average	Extreme
isoniazid	5	4 - 6
rifampicin	10	8 - 12
pyrazinamide	25	20 - 30
streptomycin*	20	15 - 25

* *Maximum : 1 g.*

RESULTS

Exclusions

Of the 427 cases of tuberculosis accepted for short treatment, 55 patients were eliminated from the analysis of results two years after the end of chemotherapy. 25 of these 55 cases were excluded before the end of the prescribed chemotherapy course, for the following reasons :

- 7 deaths : 4 due to pulmonary tuberculosis (one case of tuberculosis with multiresistant bacilli in a 14 year-old child, one case of acute miliary tuberculosis and two of meningo-miliary tuberculosis in children under 4), 3 deaths due to extra-pulmonary tuberculosis (three cases of meningitis in children under 4) ;

- 1 case of toxicity requiring an interruption of treatment for more than one month, because of pleurisy ;

- 17 other cases in which patients discontinued chemotherapy spontaneously before treatment was terminated, and disappeared : 5 cases of pulmonary tuberculosis, 8 cases of mediastinal tuberculosis, 1 of pleural tuberculosis, 3 of regional tuberculous lymphadenopathy.

30 other patients could not be followed up during the 2-year observation period prescribed at the end of treatment :

- 5 patients died of a cause other than tuberculosis (4 former pulmonary tuberculosis cases suffering from a concurrent condition : leukaemia, diabetes, haemosiderosis, systemic infection in trisomy 21 and one old case of mediastinal tuberculosis suffering from cardiomyopathy) ;

- 25 patients lost sight of during the follow-up period : all had been considered cured at the end of treatment, however.

Analysable cases

In all, status at least two years after the end of short chemotherapy was analysable in 372 cases. Of these, 369 (99 %) were defini-

tively cured : 307 with no sequelae (82.5 %), 62 with sequelae (16.5 %).

At the end of treatment, all patients were considered cured. Only three relapses were observed in the six months following the end of treatment ; all three occurred in children with pulmonary tuberculosis. The first case involved a child with initial miliary pulmonary tuberculosis, caused by drug-sensitive bacilli (isolated following gastric lavage), in whom meningitis developed three months after the end of treatment. The bacilli isolated in the cephalospinal fluid during the relapse were still sensitive to antibiotics. The 6-month regimen was repeated, with no added drugs : recovery ensued, with no pulmonary or neurological sequelae.

The other two relapses were seen in children over age 10 with initial cavitary pulmonary tuberculosis. A second, identical six-month course of chemotherapy led to recovery with limited fibrotic sequelae.

Table 23

Results two years after the end of a six-month course of chemotherapy

Localization of tuberculosis	Analysable cases at 30 months	Cure with sequelae	Cure without sequelae	Relapses 7th-12th month	Relapses 13th-30th month	Total relapses No.	Total relapses %
Pulmonary	138	98	37	3	0	3	2.2
Mediastinal	116	102	14	0	0	0	—
Pleural	49	40	9	0	0	0	—
Extra-respiratory	69	67	2	0	0	0	—
Total	372	307 + 62 = 369		3	0	3	0.8

TOLERANCE AND TOXICITY OF SHORT CHEMOTHERAPY

Tolerance of the short course of chemotherapy applied in this group was excellent. Two cases of minor skin allergy were observed, and regressed without interruption of treatment.

Hepatic toxicity was specially studied, using functional liver tests, and particularly by weekly assay of serum transaminases during the first month, then once a month or two months until the 6th month in 403 children. Disturbances were seen in 21 cases (4.6 %). Serum transáminase concentration usually rises moderately at the beginning of treatment : this rise is temporary, however, and the figures return to normal between the second and third week of treatment. Only one case of jaundice was seen. It occurred in a 10 year-old with pleural tuberculosis, who was accidentally given an excessive dose of drugs (rifampicin 17 mg/kg, isoniazid 10 mg/kg). Treatment had to be interrupted for 60 days and was resumed at normal doses with no adverse reaction until recovery.

Discussion

Short, daily chemotherapy administered for six months in children with different localizations of tuberculosis is at least as effective as the conventional 12-month course without rifampicin or pyrazina-

mide, which was previously used. Indeed, in one retrospective study of 267 cases of tuberculosis in children treated in the same unit before 1979 (including 213 cases analysed 5 years after the end of chemotherapy), the relapse rate was 6.6 %, on the average: 12 % for pulmonary tuberculosis, 3 % for pleural tuberculosis, 1.4 % for mediastinal tuberculosis and 8 % for extra-respiratory forms.

The regimen administered here was well tolerated, as a rule. The satisfactory tolerance and lack of lasting disturbance of hepatic functioning are probably explained by the fact that recommended doses were respected and that isoniazid was given in low doses, in conjunction with rifampicin. The only case of toxicity was due to accidental over-dosing.

Last, the experience with ambulatory treatment of tuberculosis in children acquired by the outpatient section of this department shows that short courses are more comfortable, less demanding and in the last analysis better accepted by patients and their family than the earlier, 12-month regimens. The major decline in the number of patients lost sight of in short treatment : 17 out of 427 (4 %) as compared to 41 out of 267 (15 %) with the 12-month course, is at least partially due to better compliance with treatment of both patients and families.

In conclusion, a short, 6-month course of chemotherapy including doses of isoniazid and rifampicin in the daily regimen may be said to be highly effective and well tolerated in children. Its application on a national scale in Algeria since 1980 has consistently corroborated the results observed on a series of young patients specially monitored in a paediatrics department in Algiers.

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CHILDHOOD TUBERCULOSIS, STILL WITH US..

1992 - N° 196-197

In recent years, much progress has been made in the control of tuberculosis, particularly since it has resorted to shorter courses of treatment.

Future prospects seem dim, however. There are two main reasons for the rising incidence of this disease : first, the development of forms with multiple resistance to the usual treatment, and secondly, AIDS, since tuberculosis is one of the opportunistic infections most frequently linked with that affliction.

In this extensive review of the many aspects of the question, an Algerian team presents the results of its many years of experience, along with international guidelines for prevention and treatment, as proposed by the International Union Against Tuberculosis and Lung Diseases and the World Health Organization.

This thorough document will provide food for thought for the many teams working in hospitals and health centres, in close contact with families and the community.

With thanks to Micheline d'Agostino - ICC for the cover illustration

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